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Kymab Ltd, a Sanofi Company

KY1005-CT05/DRI17366

A Phase IIb, Randomised, Double-blind, Placebo-controlled, Parallel Group, Multicentre Dose Ranging Study of a Subcutaneous Anti-OX40L Monoclonal Antibody (KY1005) in Moderate-to-Severe Atopic Dermatitis

21 Nov 2023

Statistical Analysis Plan

Version 3.0

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List of Abbreviations

Abbreviation	Definition
AD	Atopic dermatitis
ADA	Anti-drug antibody
ADL	Activities of daily living
ADCT	Atopic dermatitis control test
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the serum concentration curve
AUC_{last}	Area under the serum concentration curve from time 0 to the last measurable observed concentration
BLQ	Below the limit of quantification
BMI	Body mass index
BSA	Body surface area
C1q	Complement component 1q
CD	Cluster of differentiation
C_{max}	Maximum observed serum concentration
C_{min}	Minimum observed serum concentration
CI	Confidence interval
CMC	Chemistry and manufacturing controls
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRO	Contract research organisation
CTCAE	Common terminology criteria for adverse events
CTMS	Clinical trial management system
CV	Coefficient of variation
DLQI	Dermatology quality of life index
DRM	Data review meeting
EASI	Eczema area and severity index
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment

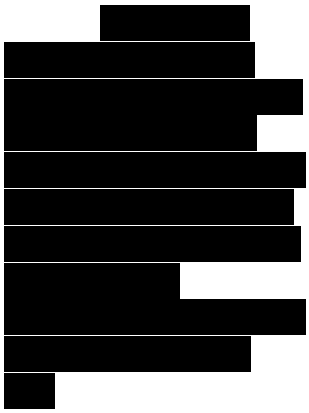
EOS	End of study
EP	Endpoint
FAS	Full analysis set
FBC	Full blood count
FSH	Follicle-stimulating hormone
GATA3	GATA binding protein 3
GCP	Good clinical practice
GDPR	General data protection regulation
GGT	Gamma-glutamyl transferase
HADS	Hospital anxiety and depression scale
Hb	Haemoglobin
HbsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HCT	Haematocrit
HIV	Human immunodeficiency virus
IA	Interim Analysis
IB	Investigator brochure
IcEv	Intercurrent event
ICH	International council for harmonisation
IDMC	Independent data monitoring committee
Ig	Immunoglobulin
IGA	Investigator global assessment
IMP	Investigational medicinal product
IRT	Interactive response technology
LDH	Lactate dehydrogenase
LoE	Lack of efficacy
LS	Least squares
LTE	Long-term extension
mAb	Monoclonal antibody
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MPV	Mean platelet volume
MedDRA	Medical dictionary for regulatory activities

MMRM	Mixed-effect model with repeated measures
NA	Not applicable
NOAEL	No observed adverse effect level
NRS	Numerical rating scale
OX40L	OX40 ligand
PBO	Placebo
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
POEM	Patient oriented eczema measure
PT	Preferred term
Q4W	Every 4 weeks
RBCC	Red blood cell count
RNA	Ribonucleic acid
RM	Rescue medication
RDW	Red cell distribution width
SAE(s)	Serious adverse event(s)
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SC	Subcutaneous(ly)
SCORAD	SCORing of atopic dermatitis
SEM	Standard error of the mean
SD	Standard deviation
SOC	System organ class
TB	Tuberculosis
TEAE(s)	Treatment emergent adverse event(s)
t_{max}	Time of maximum observed concentration
ULN	Upper limit of normal
WBCC	White blood cell count
WOCF	Worst observation carried forward
WHO	World health organisation

Version History

Table 1 Major changes in Statistical Analysis Plan

SAP version	Approval date	Changes	Rationale
1.0	25 Jan 2023	Not applicable	Original version
2.0	19 May 2023	Section 3.1: Removed redundancy in description of study design Section 4.3: Fine-tuned some analysis set definitions Section 4.4.1: Described Part 1 and Part 2 which are widely used in TLF outputs Section 4.4.5: The EASI and IGA scores from eCOA instead of IRT (stratification factor) are used Section 6.6.2: Disease-specific history clarified that it encompasses onset and duration of AD and not prior medications/treatments Section 7.1: Corrected definition of prior medications to use only start date and not requiring them to finish before randomization; added details on how information from 3 eCRF pages will be used and supplemented with categorizations external to EDC.	

3.0	21Nov2023	Section 4: Updated summary of data presentation needed for Part 1 and Part 2 Section 4.4.1: Updated definition of study periods. Section 8.3: Updated to include figures related to Week 24 and Week 52 presentation and from Week 0 to Week 52 presentation.   Section 13: New section to explain the 2 final analysis.	

1. Introduction

KY1005-CT05 (DRI17366) is a randomized, double-blind, multicenter, placebo-controlled, parallel group, Phase IIb study. The study will consist of 4 study periods: Screening period; Treatment Period 1: Baseline (Day 1) to Day 169 (Week 24); Treatment Period 2: From Day 169 (Week 24) post randomization to Day 365 (Week 52) plus 112 days of safety follow-up period.

The aim of this study is to further characterise the efficacy (including dose/exposure-response) and safety of KY1005 across a range of doses/exposures for a maximum duration of 52 weeks in adult patients with moderate-to-severe atopic dermatitis (AD) who have had an inadequate response to topical therapies or where topical therapies are not advised. This 24-week Placebo-controlled dose ranging period will be followed, in those patients who achieve an ≥ EASI 75 and/or IGA 0/1, with a randomised withdrawal period to Day 365 (Week 52) to characterise the durability of response ahead of the anticipated Phase III program.

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of clinical data collected in the study. This plan should be read in conjunction with the Amended Clinical Trial Protocol 08 Version 1.0 – 01MAR2022. All analyses will be conducted using SAS® Version 9.4 or higher.

2. Objectives

2.1. Primary objective and Endpoints

Objective	Endpoint
To characterise the efficacy (including dose/exposure-response) across a range of KY1005 exposures compared to Placebo on the signs of AD using the Eczema Area and Severity Index (EASI) in those patients who have a documented history, within 6 months prior to Baseline, of either inadequate response to topical treatments or inadvisability of topical treatments	• Percentage change in EASI from Baseline to Day 113 (Week 16).

2.2. Secondary objectives and Endpoints

Objective	Endpoint
Safety and tolerability of KY1005.	• Incidence of treatment-emergent adverse events.
The pharmacokinetic profile across a range of KY1005 doses/exposures.	• Serum KY1005 concentration assessed throughout the study.
The response across a range of KY1005 exposures on additional physician	Key secondary endpoints:

assessments of AD activity/severity (e.g. EASI 50, EASI 75, EASI 90, EASI 100, Investigator Global Assessment [IGA], SCORing of Atopic Dermatitis [SCORAD] Index and affected body surface area [BSA]).	• Percentage change from Baseline in EASI at Day 169 (Week 24). • Percentage of patients with at least a 75% reduction from Baseline in EASI (EASI 75) at Days 113 (Week 16) and 169 (Week 24). • Percentage of patients with a response of IGA 0 or 1 and a reduction from Baseline of ≥2 points at Days 113 (Week 16) and 169 (Week 24). • Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ≥4 with a Baseline pruritis NRS of ≥4 from Baseline to Days 113 (Week 16) and 169 (Week 24). <u>Other secondary endpoints:</u> • Absolute change from Baseline in EASI at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Percentage change from Baseline in EASI at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12) and 141 (Week 20). • Percentage of patients with at least a 50% reduction from Baseline in EASI (EASI 50) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Percentage of patients with at least a 75% reduction from Baseline in EASI (EASI 75) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), and 141 (Week 20). • Percentage of patients with at least a 90% reduction from Baseline in EASI (EASI 90) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Percentage of patients with at least a 100% reduction from Baseline in EASI (EASI 100) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Change in IGA from Baseline to Day 169 (Week 24) and over time. • Percentage of patients with a response of IGA 0 or 1 and a reduction from Baseline of

	≥2 points at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), and 141 (Week 20). • Absolute and Percentage change in SCORAD Index from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in affected BSA from Baseline to Day 169 (Week 24) and over time.
The response across a range of KY1005 dose/exposures on patient reported AD activity/severity (Atopic dermatitis Control Tool [ADCT], Patient Oriented [PO] Eczema Measure [POEM], Dermatology Quality of Life Index [DLQI], Hospital Anxiety and Depression Scale [HADS], and Numerical Rating Scale [NRS] for pruritus).	• Absolute and Percentage change in POEM from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in DLQI from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in ADCT from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in HADS from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in weekly average of pruritus NRS from Baseline to Day 169 (Week 24) and over time. • Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ≥3 with a Baseline pruritis NRS of ≥3 from Baseline to Days 113 (Week 16) and 169 (Week 24).
The pharmacodynamic response to KY1005 including but not limited to: The immunogenicity of KY1005, including the anti-KY1005 antibody response.	• The immunogenicity of KY1005, including the anti-KY1005 antibody response.
To explore the continued clinical response in those patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Day 169 (Week 24)	• Continued assessment of the efficacy endpoints from Day 169 (Week 24) and over time. • Time to loss of EASI 75 in participants randomised to withdrawal post-Week 24. • Time to loss of IGA 0/1 in participants randomised to withdrawal post-Week 24. • Time to loss of EASI 50 in participants randomised to withdrawal post-Week 24. • Continued assessment of patient reported AD activity/severity endpoints from Day 169 (Week 24) and over time

2.3. Exploratory Objectives and Endpoints

[redacted]

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase IIb, randomised, double-blind, placebo-controlled, parallel group, multicentre dose ranging study to characterise the efficacy and safety of SC administered KY1005 in adult patients with moderate-to-severe AD who have a documented history, within 6 months prior to Baseline, of an inadequate response to, or inadvisability of, topical treatments.

[redacted] Patients who continue to meet the eligibility criteria at Baseline will be randomised 1:1:1:1:1 to receive a SC dose of KY1005, or matching Placebo. The randomisation will be stratified by disease severity (moderate/ severe) and region at baseline. Disease Severity at baseline is defined as moderate (Baseline EASI <= 21) and severe (Baseline EASI >21). Up to 350 patients (approximately 70 patients per treatment arm) will be enrolled.

Four different SC KY1005 dosing regimens will be tested versus Placebo. From Baseline up to Day 169 (Week 24), investigational medicinal product (IMP) will be administered at the following doses and intervals; 500 mg loading dose (given as [redacted] SC administration) followed 28 days later and thereafter with 250 mg every 4 weeks (Q4W) or the following regimens from Baseline: 250 mg Q4W, or 125 mg Q4W or 62.5 mg Q4W or Placebo Q4W.

At Baseline those patients not receiving a KY1005 loading dose will receive both KY1005 and Placebo to maintain the study blind. All patients will therefore receive [redacted]SC doses at Baseline.

To enable Placebo patients and those patients randomised to the KY1005 62.5 mg Q4W, 125 mg Q4W and 250mg Q4W treatment arms to receive KY1005 at a dose expected to elicit a meaningful clinical response (based on prior clinical evidence), patients who do not achieve ≥ EASI 75 or IGA 0/1 at Week 24 will be invited to enroll in the LTE study (LTS17367) where they will receive KY1005.

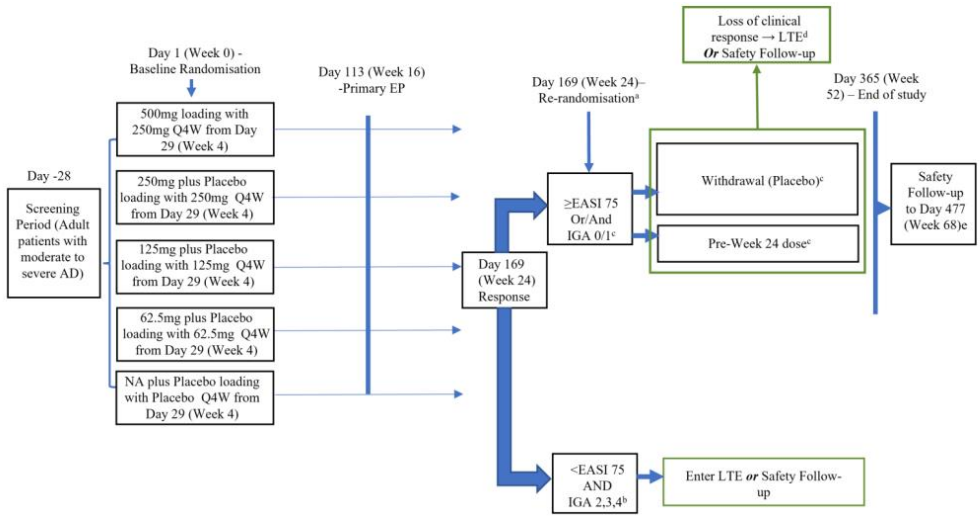
In those patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Week 24, a re-randomisation will occur pre-dose at Day 169 (Week 24) and patients will enter the second study period. The week 24 randomisation will be stratified by IGA response (IGA 0/1 or IGA 2/3/4) at week 24. This will occur irrespective of whichever dose group the patient was randomised to at Baseline including Placebo. Patients will be randomised in a 3:1 manner to be withdrawn from therapy or to continue their pre-Week 24 dose/interval. To maintain the blind, those patients randomised to the withdrawal arm will receive Placebo Q4W. [redacted]

At Day 365 (Week 52), patients who have completed the post-Week 24 period and have not experienced loss of clinical response will have an additional 112 days' safety follow-up up to Day 477 (Week 68) and then be discharged from the study. The last dose will be given no later than Day 337 (Week 48) and as such safety follow-up will be 140 days following last dose of IMP. [redacted]

The duration of the study will be up to 28 days for screening and then up to approximately Day 477 (Week 68) (to Day 365 [Week 52] plus 112 days safety follow-up, [redacted] for all patients unless enrolled into the LTE study (LTS17367) at Day 169 (Week 24) or due to loss of clinical response at or after Day 197 (Week 28). The last dose will be given no later than Day 337 (Week 48).

The IMPs are KY1005 (SAR445229), hereby known as KY1005, or matching Placebo.

Figure 1 Study Design



AD=atopic dermatitis; IMP=investigational medicinal product; EP=endpoint; EASI=eczema area and severity index; IGA= investigator global assessment; LTE=long-term extension; Q4W=every 4 weeks; NA=not applicable.
On Day 169 (Week 24), patients are re-randomised prior to IMP administration on the basis of their Day 169 (Week 24) response.

3.2. Treatments

KY1005

[redacted]

Matching Placebo

[redacted]

4. General Statistical Considerations

Continuous data will be summarized using descriptive statistics (i.e., n, mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be summarized using the patient count and percentage in each category.

For Part 1:
The data in Part 1 will be presented according to planned treatment or actual treatment received at Day 1. These analyses include the following: patient disposition, demographics and baseline characteristics, significant protocol deviations, medical history, drug exposure, prior/concomitant medications for AD and non-AD, rescue and prohibited medications and procedures impacting efficacy, rescue medications, prohibited medications and procedures, concomitant procedures, adverse events, injection site reactions, efficacy parameters (EASI, IGA, NRS etc), 12-lead electrocardiogram parameters, laboratory parameters, PK parameters, and ADA.

For Part 2:
The data in Part 2 will be presented according to treatment sequence planned or received. These analyses include the following: drug exposure, prior/concomitant medications for AD and non-AD, rescue and prohibited medications and procedures impacting efficacy, rescue medications, prohibited medications and procedures, concomitant procedures, adverse events, injection site reactions, efficacy parameters (EASI, IGA, NRS etc), 12-lead electrocardiogram parameters, laboratory parameters, PK parameters, and ADA. Patient disposition, demographics and baseline characteristics, significant protocol deviations, and medical history will be presented among patients enrolled in Part 2. Data on some endpoints such as prior/concomitant medications for AD and non-AD, rescue and prohibited medications and procedures impacting efficacy, rescue medications, prohibited medications and procedures, concomitant procedures, efficacy adverse events, laboratory parameters, PK and ADA will be presented from baseline up to Week 52 or Week 68 among patients enrolled in Part 2. In addition, presentation of rescue and prohibited medications and procedures will also be done for Week 52 to Week 68 data only.

All CIs presented will be 95% (two-sided) CIs.

Non-zero percentages will be rounded to one decimal place. When count data are presented, percentages will be rounded to one decimal place. If count is 0, the percentage will not be presented. CI will be presented to two decimal places for proportion, wherever applicable. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values.

The denominator for all percentages will be the number of patients with non-missing values of corresponding parameter in that treatment within the analysis population of interest, unless otherwise specified.

For the summary statistics of all numerical variables, unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported up to a maximum of three decimal places. Mean and median will be displayed to one level of precision greater than the data collected up to a maximum of three decimal places. Standard deviation / standard error will be

displayed to two levels of precision greater than the data collected up to a maximum of three decimal places.

A table, figure, listing is to be generated for any required item even where no data is available or reported. This will ensure the health authorities that the tables, figures, listings and narratives are accounted for. This table, figure or listing will state: "No Data Reported".

All other statistical analyses performed in part 1 will be performed using a two-sided hypothesis test at the overall 5% level of significance.

P-values will be rounded to four decimal places. If a rounded P-value is less than 0.0001 it will be reported as "<0.0001."

Unless otherwise specified, baseline will be defined as the last non-missing evaluation prior to study drug administration.

Calculation of Change and Percent Change from Baseline

Change from Baseline to any trial Week t (C_t) is calculated as follows:

$C_t = M_t - M_B$, where:

- M_t is the measurement of interest at Week t
- M_B is the measurement of interest at Baseline

Percent change from Baseline to any trial Week t (P_t) is calculated as follows:

$P_t = 100*(Ct/MB)$

4.1. Sample Size

A sample size of 350 patients (70 patients / group) in the target population, (adult with moderate-to-severe AD who have a documented history, within 6 months prior to Baseline, of either inadequate response to topical treatments or inadvisability of topical treatments), randomised 1:1:1:1:1 to four KY1005 groups or matching Placebo group is estimated to provide at least [redacted] power to detect a pairwise difference in means between each KY1005 and Placebo with respect to the percentage change in EASI from Baseline to Day 113 (Week 16), based on a 2-sided 2-sample equal-variance t-test.

[redacted]

4.2. Intercurrent Event

Intercurrent events relevant for this study are presented in table below:

Table 2 Intercurrent Event Types

4.3. Analysis Set

The following analysis sets will be used in the statistical analyses.

4.3.1. All Enrolled Set

All Enrolled Analysis Set includes all patients who signed an informed consent form with no screen failures. Analysis will be based on treatment allocated at randomisation.

4.3.2. Full Analysis Set for Part 1

The Full Analysis Set (FAS1) for Part 1 includes all randomised patients up to week 24. Efficacy analysis will be based on treatment allocated at randomisation.

4.3.3. Full Analysis Set for Part 2

The Full Analysis Set (FAS2) for Part 2 includes all re-randomised patients at Week 24 up to week 52. Efficacy analysis will be based on treatment allocated at re-randomisation.

4.3.4. Safety Analysis Set for Part 1

The safety set (SAF1) for Part 1 will consist of all patients who take at least one dose of study treatment, including Placebo up to week 24. Any analysis based on the SAF1 will be based on the treatment actually received, regardless of assigned treatment according to the planned randomisation.

4.3.5. Safety Analysis Set for Part 2

The safety set (SAF2) for Part 2 will consist of all re-randomised patients at Week 24 who take at least one dose of study treatment on or after Week 24. Any analysis based on the SAF2 will be based on the treatment actually received at week 24, regardless of assigned treatment according to the planned randomisation.

4.3.6. Pharmacokinetic Set for Part 1

The PK set will consist of all randomized patients in the SAF1 with at least one post-Baseline PK sample (with adequate documentation of dosing and sampling dates and times) up to week 24. Any analysis based on the PK1 will be based on the treatment actually received, regardless of assigned

treatment according to the planned randomisation. Patients who received only placebo will not be included.

4.3.7. Pharmacokinetic Set for Part 2

The PK set will consist of all randomized patients in the SAF2 with at least one post-Baseline PK sample (with adequate documentation of dosing and sampling dates and times) from Week 24 up to week 52. Any analysis based on the PK2 will be based on the treatment actually received at week 24, regardless of assigned treatment according to the planned randomisation. Patients who received only placebo will not be included.

4.3.8. Anti-drug Antibody Set for Part 1

The ADA set will consist of all randomized patients treated with KY1005 in the SAF1 with at least one post-Baseline ADA result (positive, negative or inconclusive) up to week 24. Any analysis based on the ADA1 will be based on the treatment actually received, regardless of assigned treatment according to the planned randomisation.

4.3.9. Anti-drug Antibody Set for Part 2

The ADA set will consist of all randomized patients treated with KY1005 in the SAF2 with at least one post-Baseline ADA result (positive, negative or inconclusive) from Week 24 up to week 52. Any analysis based on the ADA2 will be based on the treatment actually received at week 24, regardless of assigned treatment according to the planned randomisation.

4.4. Other Important Considerations

4.4.1. Definition of Study Period to be evaluated

For the purposes of efficacy and safety data analysis, and for reporting, the following study periods are considered:

- Part 1:
  - For efficacy data, this is the induction phase which encompasses data from baseline through week 24 visit.
  - For non-efficacy data, this is the induction phase which encompasses data from baseline through end of study involvement for patients who did not proceed to Part 2 or first IMP date or rerandomization date in Part 2 for patients who proceed to Part 2.
- Part 2:
  - For efficacy data, this is the maintenance phase which encompasses data from week 24 up to week 52 visit.
  - For non-efficacy data, this is the maintenance phase which encompasses data from first IMP date or rerandomization date in Part 2 up to week 68. For rescue and prohibited medications and procedures impacting efficacy, this includes data from first IMP data or rerandomization date in Part 2 up to week 52.
- Overall:
  - For efficacy data, this is the period covering from baseline to week 52 visit.
  - For safety data, this is the period covering from baseline through end of study involvement for patients who did not proceed to Part 2 or up to week 68 for

patients who proceed to Part 2. For rescue and prohibited medications and procedures impacting efficacy, this includes data up to week 52 only.

For efficacy analysis, all observed measurements will be eligible to be included in analyses.

4.4.2. Windows Periods

Before analyzing the data, all post-Baseline visits (scheduled or unscheduled, unless specified otherwise) will be mapped to an analysis visit based on the windowing algorithm in Section 15.5 Analysis window Details. If multiple visits containing the same data of interest can be mapped to the same analysis visit, the visit closest to the target day will be used in the analysis. In the event that two or more visits are equidistant to the target day, the later visit will be used in the analysis.

Please refer Section 0 for details of Analysis Window.

4.4.3. Definition of Baseline

Baseline value is the last available value prior to the first dose of study drug or randomization date, in case patient is not exposed. The baseline for weekly average pruritus NRS score is defined as the average of daily non-missing scores obtained during the 7 days prior to randomization. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score

4.4.4. Study Day Calculation

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for patient not exposed).
If the event is after the reference start date (date of drug administration) then the study day will be calculated as assessment date – date of drug administration + 1 else if event is prior to the reference start date then it will be calculated as assessment date – date of drug administration.
Summary statistics for data such as adverse events and concomitant medications will not be reported by visit.

4.4.5. Pre-specified Subgroups

The following subgroups will be explored for the primary endpoint and selected key secondary endpoints:

1. Age (<65, >=65)
2. Gender (male, female)
3. Race
4. Region (ASIA-PACIFIC, EMEA, NORTH AMERICA)
5. Weight (<median, >=median)
6. EASI (<=21 vs >21) from eCOA, per baseline definition in Section 4
7. IGA (3 vs 4) from eCOA, per baseline definition in Section 4
8. Previous systemic immunosuppressant use (Yes vs No)
9. Previous biologic use (Yes vs No)
10. Previous dupilumab use (Yes vs No)
11. Previous cyclosporine use (Yes vs No)
12. Previous methotrexate use (Yes vs No)

4.4.6. Duration (e.g., for Adverse Events)

If date is collected, then duration is calculated as event end date minus event onset date + 1. Unit is days.

4.4.7. Coding Dictionaries

Adverse events, medical history and prior and concomitant non-drug treatment procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1 or later.

Previous and concomitant treatments will be coded with the WHODRUG Global B3 March 2021 or later.

4.4.8. Efficacy Parameters

Below efficacy parameters will be analyzed:

1. Eczema Area and Severity Index (EASI)

The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin 2001). The EASI score calculation is based upon the Physician's Assessment of Individual Signs [erythema (E), induration/papulation (I), excoriation (X), and lichenification (L)], where each sign is scored as 0 = Absent, 1 = Mild, 2 = Moderate, or 3 = Severe, and also upon the Area Score [based on the % (BSA) affected] where 0 = 0% BSA, 1 = 1-9% BSA, 2 = 10-29% BSA, 3 = 30-49% BSA, 4 = 50-69% BSA, 5 = 70-89% BSA, 6 = 90-100% BSA.

For each of major section of the body (head, upper extremities, trunk and lower extremities), EASI score = (E+I+X+L) x Area Score. The total EASI score is the weighted total of the section EASI using the weights 10% = head, 20% = upper extremities, 30% = trunk, 40% = lower extremities. The minimum possible EASI score is 0 and the maximum possible EASI score is 72 where a higher score indicates increased extent and severity of atopic dermatitis. The EASI score of each sign (E, I, X and L) can be calculated in a similar way, for example, the EASI score of erythema = weighted sum of E x Area Score at each section

2. Investigator's Global Assessment (IGA)

The IGA is a static 5-point measure of AD disease severity used in clinical studies to determine severity of AD and clinical response to treatment. The ratings (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) are an overall assessment of AD skin lesions based on erythema and papulation/infiltration. IGA score will be assessed at every scheduled and unscheduled clinic visit.

3. Pruritus Numeric Rating Scale (NRS)

The NRS for pruritus is an assessment tool that will be used to assess the patient's worst itch as a result of their AD in the previous 24 hours. This will be recorded daily, ideally in the morning, using an internet-enabled device with patients asked, "On a scale of "0" (no itch) to "10" (worst imaginable itch), how was your worst itch in the past 24 hours?". Patients will additionally be asked to record NRS for 7 consecutive days immediately prior to Baseline. Sites will be encouraged to contact patients who have missed 2 consecutive e-diary entries to encourage patient compliance.

The baseline for weekly average pruritus NRS score is defined as the average of daily non-missing scores obtained during the 7 days prior to randomization (Day –6 to Day 1). A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. The post-baseline weekly average pruritus NRS score is calculated as the average of daily non-missing scores obtained from the reported daily NRS within the week up to and including target day of the scheduled visit.

4. SCORing of Atopic Dermatitis Index

The SCORAD Index is a validated clinical tool developed to standardise the evaluation of the extent and severity of AD [SCORAD Dermatol Basel Switz 1993]. This assessment will be completed using an internet-enabled device. To determine the extent of AD, the affected area (A) as a percentage of the whole body is determined, with a maximum score of 100% (head and neck [9%], upper limbs [9% each], lower limbs [18% each], anterior trunk [18%], back [18%], genitals [1%]). The severity (B) of 6 specific symptoms of AD (redness, swelling, oozing/crusting, scratch marks, skin thickening [lichenification], dryness [area where there is no inflammation]) is assessed on a 4 point scale, with a maximum score of 18: none (0), mild (1), moderate (2) or severe (3). Patientive symptoms (ie, itch and sleeplessness; C) are recorded as scored by the patient or relative on a visual analogue scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20.

The SCORAD score for each patient is calculated as: A/5 + 7B/2 + C.

5. Body Surface Area Involvement of Atopic Dermatitis

Body surface area (BSA) affected by AD will be assessed for each section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined.

6. Patient Oriented Eczema Measure

The POEM is a tool used for monitoring atopic eczema severity. It focuses on the illness as experienced by the patient. This will be completed using an internet enabled device.
The questionnaire consists of 7 questions pertaining to the symptoms of AD and their frequency. Scores are based on a scale of zero (no days) to 4 (every day in the last week) for each question, with a maximum score of 28 possible for all questions. A POEM total score is correlated to eczema severity (0 2 [clear or almost clear], 3 7 [mild], 8 16 [moderate], 17 24 [severe], 25 28 [very severe]).

7. Dermatology Life Quality Index

The DLQI is a dermatology specific QoL instrument and is a simple, validated questionnaire. This will be completed using an internet enabled device.

The instrument consists of 10 questions pertaining to the effect of AD on QoL. Scores are based on a scale of “0” (not at all/not relevant/question unanswered) to “3” (very much/prevented work

or studying), with a maximum score of 30 possible for all questions. The total score is correlated to the detrimental effect of AD on QoL (0 1 [no effect at all on patient's life], 2 5 [small effect], 6 10 [moderate effect], 11 20 [very large effect] and 21 30 [extremely large effect]).

8. Atopic Dermatitis Control Tool

The ADCT is a validated 6-item instrument with a 7-day recall period to measure AD disease control. This will be completed using an internet enabled device. The following domains are assessed: overall severity of symptoms, frequency of intense episodes of itching, severity of bother of itching, frequency of sleep impact, severity of daily activities impact, severity of mood or emotions impact. Each item is scored from 0 (none) to 4 (extreme). A total score of 7 or more points (derived by adding item scores) was identified during validation as an optimum threshold to identify patients whose AD is "not in control".

9. Hospital Anxiety and Depression Scale

The HADS is a validated 14-item PRO measure used to assess states of anxiety and depression over the past week. This will be completed using an internet enabled device. Only the HADS total score will be presented in the analysis

5. Patient Disposition

5.1 Disposition

Patient disposition will be summarized by study treatment group and overall.

Disposition of patients includes the counts and percentages of patients for the following categories: screened, screen failures, randomized, patients who completed the study treatment, patients who discontinued from the study treatment, patients who completed the study, patients who discontinued from the study, patients who completed Week 24, patients re-randomised at Week 24, number of patients who enter in LTE, patients who discontinued from study treatment prior to Week 24, patients who discontinued from study prior to Week 24, and patients who provide consent for the skin biopsy sub-study. For patients who discontinue treatment prior to week 24 or discontinue study prior week 24, the denominator will be the number of patients randomized for part 1. For screened and screen failure, only the total count will be provided.

Similar disposition items will be summarized for Part 2, treatment completion, early discontinuation from treatment, study completion, early discontinuation from study, etc. The denominator for Part 2 disposition table will be the number of patients that were re-randomized at Week 24.

The primary reasons for study and treatment discontinuation will be also provided.

Study analysis population will be summarized for Part 1 by Part 1 randomization arms; for Part 2 by Week 24 re-randomization treatment arms.

Any discontinuation due to COVID-19 will also be summarized.

Patient disposition and discontinuation data will be presented in a listing.

5.2 Protocol Deviations

Deviations from the protocol will be recorded in clinical trial management system (CTMS).

Significant/non-significant protocol deviations will be presented in a summary table using counts and percentages by protocol deviation category for the FAS. All protocol deviations will be listed with date of occurrence, deviation category and deviation description.

All protocol deviations from COVID-19 positive patients will be listed with date of occurrence, deviation category and deviation description separately.

5.3 Inclusion and Exclusion Criteria

The details of Inclusion and Exclusion criteria are listed in Section 4.2 and 4.3 of the protocol. For patients who did not satisfy these criteria, the inclusion and exclusion criteria will be listed with the deviation.

6. Demographics and Baseline Characteristics

6.1 Demographics

The analysis will be based on the FAS1 & FAS2 and the SAF1 & SAF2 for Part 1 and Part 2, respectively.

The demographics and baseline characteristics will be presented in tables using descriptive statistics. The demographic characteristics consist of age (Years), sex, race, ethnicity. The baseline characteristics consist of height (cm), weight (kg) and body mass index (BMI [kg/m^2]), disease severity, region, EASI score (IRT and eCRF data), IGA, pruritus NRS, BSA, SCORAD, POEM, DLQI, HADS, ADCT collected at baseline. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for age, height, weight and BMI at baseline will be calculated overall and by treatment group. The counts and percentages of patients by sex (male, female), ethnicity, race, disease severity (moderate/severe) and region will be calculated overall and by treatment group. Percentages will be based on the total number of patients in each treatment group.

Patient demographic and baseline characteristics will be presented in a listing.

6.2 Medical History

6.2.1 General Medical History

Medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 or later.

The data for medical history will be summarized with counts and percentages of patients overall and by treatment group. Patient general medical history data including specific details will be presented in a listing. The analysis will be based on the FAS1 and the SAF1 for Part 1 and FAS2 for Part 2.

6.2.2 Disease-Specific History

Duration of AD calculated as time from onset to randomization, disease severity at baseline as determined by EASI and IGA at baseline (both per IRT and eCOA) will be persented in demography and baseline characteristics outputs.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

All medications/vaccinations will be coded according to the World Health Organization drug dictionary (WHODRUG Global B3 March 2021 or later).

Prior medications refer to medications that started any time prior to first dose of study treatment or randomization if that is not available regardless of the end date. AD treatments include systemic and non-systemic corticosteroids, systemic and non-systemic calcineurin inhibitors, and systemic and non-systemic treatment for AD or other indications with an immunosuppressive/immunomodulating substance including (but not limited to) dupilumab, JAKi and aIL13 mABs. Treatments given to AD will be collectively analyzed from all applicable eCRF pages: Concomitant Medications, Prior and Current Systemic and Topical Treatments for AD.

Concomitant medications refer to medications started prior to AND continued after the first dose of study treatment or taken any time after the first dose of study treatment up to the follow-up visit.

The prior and concomitant medications will be summarized separately. At each level of summarization, a patient is counted once if he/she reports one or more medications at that level. Drug class will correspond to the Anatomical Therapeutic Classification (ATC) Level 4 term or other AD-specific, WHODRUG-based classification.

All prior medications will be summarized using counts and percentages.

All concomitant medications will be summarized using counts and percentages for the FAS1 and FAS2 for Part1 study and Part 2 study respectively.

The imputation algorithm for partial and missing medication dates is provided in Appendix 15.2.

All prior and concomitant medications will be presented in a listing.

7.2. Permitted Concomitant Medications

Other than the prohibited medications listed in Section 7.3, treatment with concomitant medication is permitted during the study. This includes treatment with oral contraceptives, nasal, otological, intraarticular and inhaled corticosteroids for any duration, and oral or topical antibiotics for up to 2 weeks for AD-associated superficial skin infections.

7.3. Prohibited Concomitant Medications (and Procedures)

Treatment with the following concomitant medications is prohibited during the study:

- Dupilumab.
- Topical or systemic tacrolimus and pimecrolimus (exceptions might apply per protocol).
- Topical or systemic corticosteroids (exceptions might apply per protocol, e.g. topical steroids used for rescue purpose).
- Leukotriene inhibitors.
- Allergen immunotherapy.
- Systemic treatment with an immunosuppressive/immunomodulating substance (including, but not limited to aIL13 mABs, JAKi, aOX40 mAbs, cyclosporine, mycophenolate-mofetil, IFN-γ, azathioprine, methotrexate, or biologics).
- [redacted].

The following concomitant procedures are prohibited during study participation:

- Elective surgical procedures.
- Ultraviolet (UV) procedures (phototherapy [narrowband UVB, UVB, UVA1 or psoralen UVA]).
- Tanning in a booth/parlour.
- More than 2 bleach baths per week.

7.4. Rescue Medications

AD rescue therapy is not permitted in the first 14 days following randomisation. Any AD rescue therapy administration either topical or systemic during this period will result in permanent discontinuation from the IMP. Bland emollients are not considered rescue therapy for AD, and should be maintained during this period as per protocol.

If medically unavoidable after Day 14 (ie, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the Investigator. For the purpose of efficacy analysis, patients who receive rescue topical treatment during this study treatment period will be considered treatment failures but can continue study treatment if the rescue treatment consists of topical medications only.

If topical corticosteroids (TCS) are needed, it is recommended that the investigator start with the least potent TCS for the face (eg, hydrocortisone 2.5% cream/ointment) and moderately potent TCS for the body (eg, triamcinolone acetonide 0.1% cream/ointment), applied up to twice daily. Where the use of moderate potency topical corticosteroids (TCS) is not considered clinically appropriate, low potency TCS or topical calcineurin inhibitors can be used, however, these should be reserved for problem areas only. Topical PDE4 inhibitors are also permitted.

Patients should use topical rescue therapy only for as long as necessary to control problem areas on a maximum of 2 occasions during study participation, and for a maximum of 2 consecutive weeks on each occasion.

If a patient receives rescue treatment with high potency TCS, systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc) or receives more than 2 episodes of topical rescue treatment, study treatment will be immediately discontinued.

Investigators should conduct efficacy and safety assessments immediately before administering any rescue treatment. An unscheduled visit may be required.

All patients should complete the schedule of study visits and assessments whether or not they complete study treatment and whether or not they receive rescue treatment for AD. If a patient has IMP permanently discontinued due to the taking of systemic therapy rescue but consent is retained, study assessments may be continued until Day 169 (Week 24) for patients who discontinue IMP in the first study period, or until Day 365 (Week 52) or the end of the safety follow-up period (whichever is longer) in patients who discontinue IMP after Day 169 (Week 24).

Rescue medication will be coded according to the World Health Organization drug dictionary (Global B3 March 2021 or later). Drug class will correspond to the Anatomical Therapeutic Classification (ATC) Level 4 term or other AD-specific, WHODRUG-based classification.
The data will be summarized using counts and percentages by preferred drug name for each treatment group and overall. At each level of summarization, a patient is counted once if the patient reported more than one medication. The analysis will be based on FAS1 & FAS2 for Part 1 and Part 2, respectively.

A listing of rescue medications will be presented.

A blinded medical review of rescue/prohibited treatments will be implemented before or at the time of each database lock by considering the type of medication, indication, timing, frequency and the potential impact of the use of the prohibited medication or procedure on efficacy. Categorization of medications performed within the frame of this review will be the basis of related intercurrent event determination in line with the estimand strategy in Section 8.

7.5 Study Treatments

7.5.1 Extent of Exposure

Drug exposure is defined as the total number of weeks + 28 days a patient is exposed to study treatment. Duration of exposure (weeks) in Part 1 is derived as (Last dose date in Part 1 - First dose date in Part 1 + 1)/7 + 4 weeks. Duration of exposure (weeks) in Part 2 is derived as (Last dose date in Part 2 - First dose date in Part 2 + 1)/7 + 4 weeks. The duration of exposure and dose will be summarized in a table by treatment group and overall, using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). The number and percentages of patients

for the cumulative duration of exposure will be presented for below categories: ≥ 4 weeks, ≥ 8 weeks, ≥ 12 weeks, ≥ 16 weeks, ≥ 20 weeks, ≥ 24 weeks (and ≥ 28 weeks for Part 2 study only). Study treatment administrations will be summarized and listed by treatment group in the main period and transition.

The analysis will be based on SAF1 & SAF2 for Part 1 and Part 2, respectively.

7.5.2 Treatment Compliance and Modifications

The overall compliance by treatment group will be summarized descriptively. For each patient, the compliance will be calculated as the total amount of actual drug administered divided by the expected number of drug administered which is 2 injections per subject at baseline followed by 1 injection Q4W onwards.
The compliances will then be classified into one of the following categories: <80%, 80% –<100%, and ≥100% and will be presented as the number and percentage of patients in each category. Descriptive statistics will be provided for overall compliance, for each treatment group. Percentages will be computed using the number of patients in each treatment group. A summary of each patient's compliance will be presented in a listing.

The analysis will be based on SAF1 & SAF2 for Part 1 and Part 2, respectively.

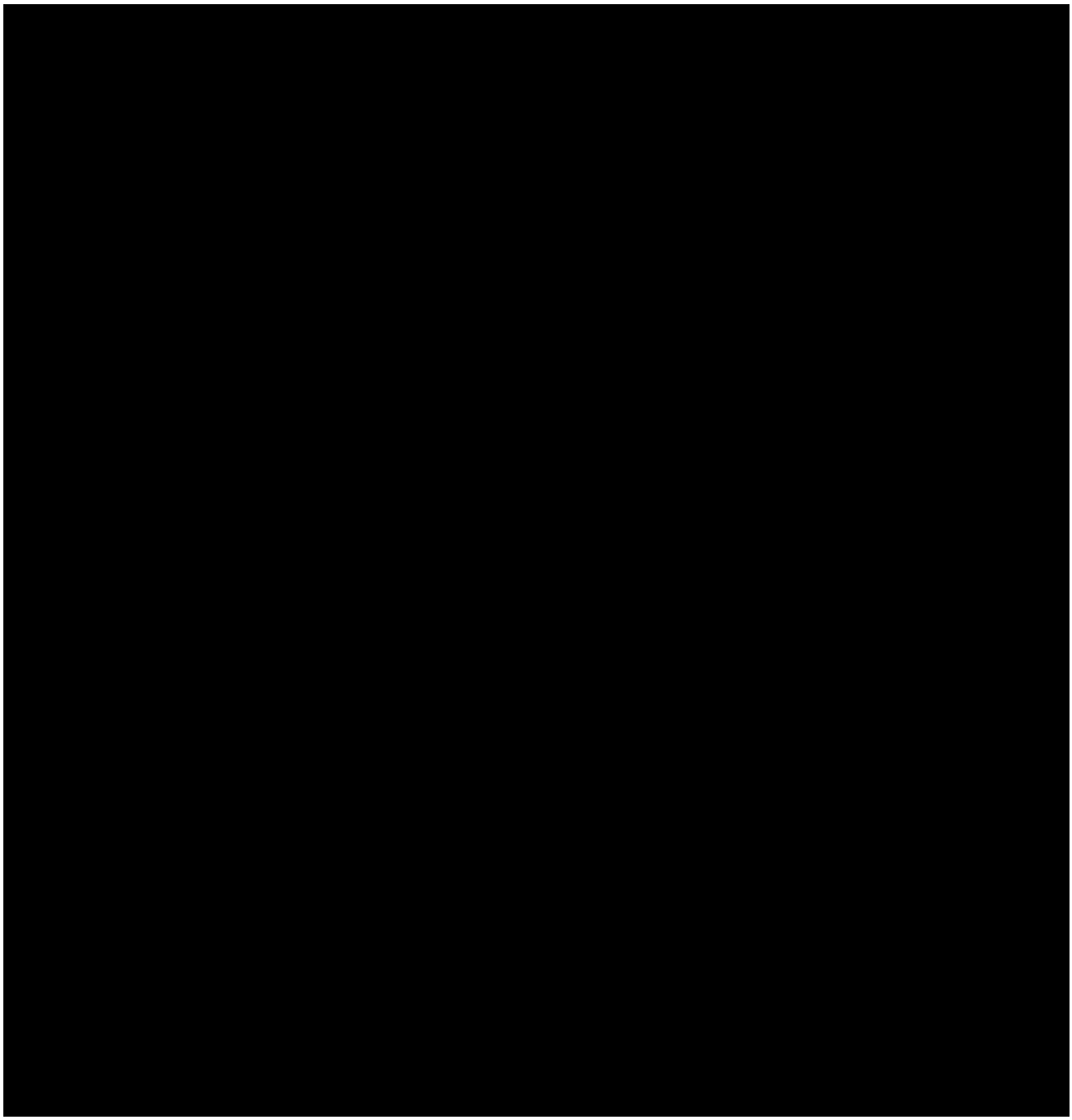
8. Efficacy Analysis

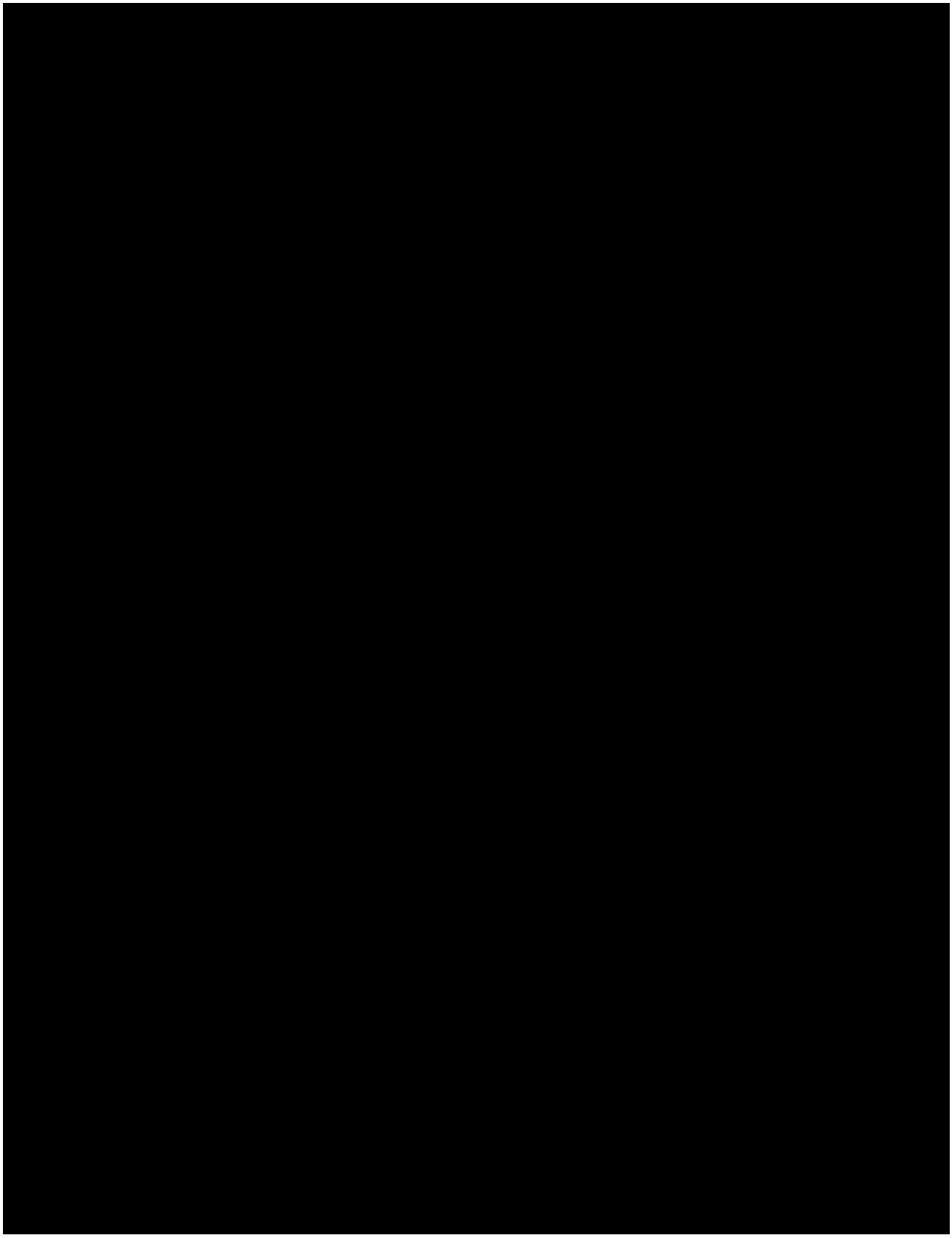
8.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage change in EASI from baseline to Day 113 (Week 16).

The primary analysis will be conducted on the FAS1 after all randomized patients have reached the Day 169 (Week 24) visit/early termination.

Table 3 Estimands and Strategies for Managing Intercurrent Events for Primary Endpoint





[redacted]

Multiple imputation will be performed using the imputation method described in the tipping point analysis section given below (Steps 1, 2 and 5).

Tipping point analysis

[redacted], a tipping point analysis will be performed for the primary endpoint with imputed missing Week 16 values as follows:

- Step 1. Monotone missing pattern will be induced by Markov Chain Monte Carlo (MCMC) method using PROC MI, with seed=293874: for patients who have intermediate missing values, the intermediate missing values will be imputed assuming a multivariate normal distribution over observations from all visits. 40 datasets with a monotone missing pattern will be obtained using this method.
- Step 2. For each of the imputed dataset with monotone missing pattern obtained in Step 1, the remaining missing data will be imputed using the regression method for the monotone- pattern, with seed=293874 with adjustment for covariates including response variable, intervention groups, randomisation strata (region, disease severity), and baseline value of the corresponding endpoint. All available data in the monotone missing pattern data will be used. One imputed dataset will be obtained for each of the imputed dataset at Step 1. So, 40 fully imputed datasets will be obtained altogether.
- Step 3. The imputed values in each KY1005 dose arm are added by a positive amount d for each imputed data set.
- Step 4. The imputed values in placebo group are subtracted by a positive amount p for

each imputed data set.

- Step 5. Change from baseline in endpoint will be analyzed using ANCOVA model same as the one in primary analysis. Then, the SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the 40 analyses using Rubin's formula.

Step 3 to Step 5 will be repeated iteratively until the p-value for treatment effect of each KY1005 dose arm compared to placebo estimated in Step 5 is >0.05.
Summary of EASI values, absolute and percent change from baseline values at scheduled visits will be provided. Line plots will be provided. Further details please refer to Section 8.3.

Subgroup analysis of primary endpoint

The primary efficacy endpoint will also be analysed for the pre-specified subgroups as specified in Section 4.4.5. The analyses for the subgroup population will be performed with the primary Estimand (Estimand 1) for the primary endpoint regarding the intercurrent events and missing data handling, and population level summary. In each subgroup, the treatment effects for the primary endpoint will be provided, as well as the corresponding 95% CI.

Interaction effects will be tested using the ANCOVA model between treatment arms and subgroup factor. The model will include all the covariates in the main statistical model plus the subgroup variable and the subgroup-by-treatment interaction. A p-value for the test of interaction will be provided.

Forest plot will be provided to present the estimates and the corresponding 95% CI for each subgroup.

Multiplicity control

[redacted]

8.2 Analysis of Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints for the study are:

- Percentage change from baseline in EASI at Day 169 (Week 24).
- Percentage of patients with at least a 75% reduction from baseline in EASI (EASI 75) at Days 113 (Week 16) and Day 169 (Week 24).
- Percentage of patients with a response of IGA 0 or 1 and a reduction from baseline of ≥2 points at Days 113 (Week 16) and Day 169 (Week 24).
- Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ≥4 with a baseline pruritis NRS of ≥4 from baseline to Days 113 (Week 16) and Day 169 (Week 24).

Analysis for continuous key secondary endpoint

Below Estimands will be applied to analyze the continuous key secondary endpoint: Percentage change from baseline in EASI at Day 169 (Week 24). Please refer the details in Section 15.1 in Appendices. For analysis approach with multiple imputation, same multiple imputation process described for primary endpoint will be applied for the continuous key secondary endpoint.

- Estimand 4a description: The mean difference in percentage change from baseline in EASI to Day 169 (Week 24) of 4 different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.

  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 1 (Table 3 Estimands and Strategies for Managing Intercurrent Events for Primary Endpoint**Table 3**, Column 2).

- Estimand 4b description: The mean difference in percentage change from baseline in EASI to Day 169 (Week 24) of 4 different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.

  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 2 (Table 3 Estimands and Strategies for Managing Intercurrent Events for Primary Endpoint**Table 3**, Column 3).

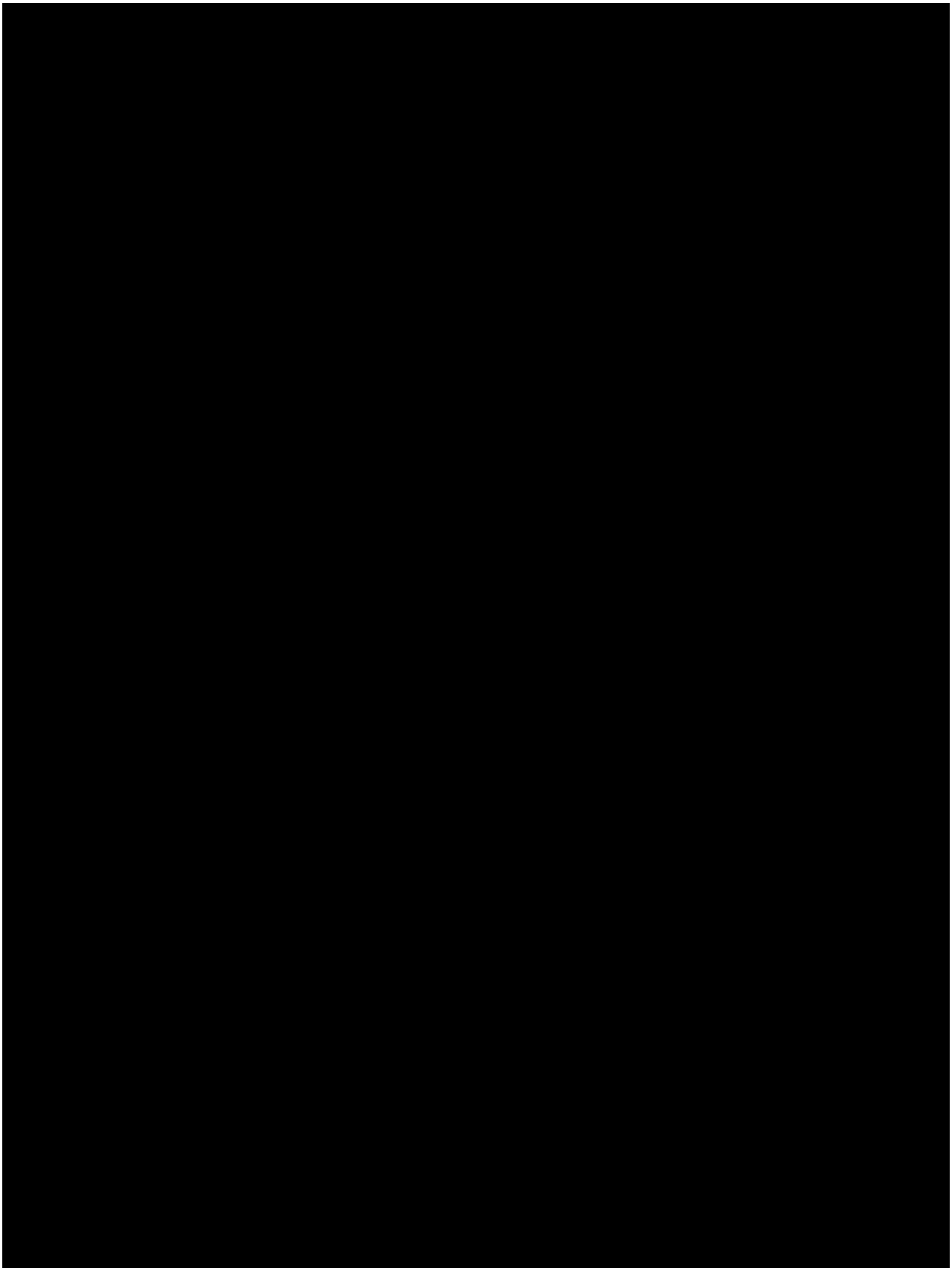
- Estimand 4c description: The mean difference in percentage change from baseline in EASI to Day 169 (Week 24) of 4 different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.

  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 3 (Table 3 Estimands and Strategies for Managing Intercurrent Events for Primary Endpoint**Table *3***, Column 4).

Analysis for binary key secondary endpoints

Table 4 Estimands and Strategies for Managing Intercurrent Events for Binary Key Secondary Endpoint

[redacted]



[redacted]

- Estimand 5c description: The Proportion of patients with EASI 75 at Day 169 (Week 24) for different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.
  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 5a (Table 4, Column 1).

- Estimand 5d description: The Proportion of patients with EASI 75 at Day 169 (Week 24) for different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.
  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 5b (Table 4 Column 2).

- Estimand 6a description: The Proportion of patients with IGA 0/1 and a reduction from baseline of ≥2 points at Day 113 (Week 16) for 4 different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.
  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 5a (Table 4, Column 1).

- Estimand 6b description: The Proportion of patients with IGA 0/1 and a reduction from baseline of ≥2 points at Day 113 (Week 16) for 4 different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.
  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 5b (Table 4, Column 2).

- Estimand 6c description: The Proportion of patients with IGA 0/1 and a reduction from baseline of ≥2 points at Day 169 (Week 24) for different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.
  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 5a (Table 4, Column 1).

- Estimand 6d description: The Proportion of patients with IGA 0/1 and a reduction from baseline of ≥2 points at Day 169 (Week 24) for different KY1005 dosing regimens compared to placebo,

[redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.
The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 5b (Table 4, Column 2).

- Estimand 7a description: The Proportion of patients with improvement of weekly average of pruritus NRS ≥4 from baseline at Day 113 (Week 16) for 4 different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.
  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 5a (Table 4, Column 1).

- Estimand 7b description: The Proportion of patients with improvement of weekly average of pruritus NRS ≥4 from baseline at Day 113 (Week 16) for 4 different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.
  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 5b (Table 4, Column 2).

- Estimand 7c description: The Proportion of patients with improvement of weekly average of pruritus NRS ≥4 from baseline at Day 169 (Week 24) for different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.
  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 5a (**Table *4***Table 4, Column 1).

- Estimand 7d description: The Proportion of patients with improvement of weekly average of pruritus NRS ≥4 from baseline at Day 169 (Week 24) for different KY1005 dosing regimens compared to placebo, [redacted] in adult patients with moderate to severe AD who have had inadequate response to topical treatments or inadvisability of topical treatment.
  The analysis of the key secondary endpoint and the handling of intercurrent events and missing data will be performed similar to Estimand 5b (Table 4, Column 2).

  Summary of binary key secondary efficacy endpoints at scheduled visits will be provided. Bar plots will be provided. Further details please refer to Section 8.3.

  <u>Subgroup analysis of key secondary endpoints</u>
  The following key secondary efficacy endpoints will also be analysed for subgroups analysis, using the same subgroups as for primary efficacy endpoint.

- Percentage of patients with at least a 75% reduction from baseline in EASI (EASI 75) at Days 113 (Week 16).
- Percentage of patients with a response of IGA 0 or 1 and a reduction from baseline of ≥2 points at Days 113 (Week 16).

The analyses for the subgroup population will be performed using primary Estimand for the corresponding key secondary endpoint (Estimand 5a, 6a respectively). Forest plots will be provided to present the estimates and the corresponding 95% CI for each subgroup.

8.3 Analysis of Other Secondary Efficacy Endpoints

Below are the additional other secondary efficacy endpoints for the study:

- Absolute change from baseline in EASI at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24).
- Percentage change from baseline in EASI at Days 15 (Week 2); 29 (Week 4), 57 (Week 8), 85 (Week 12) and 141 (Week 20).
- Percentage of patients with at least a 50% reduction from baseline in EASI (EASI 50) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24).
- Percentage of patients with at least a 75% reduction from baseline in EASI (EASI 75) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85(Week 12) and 141 (Week 20).
- Percentage of patients with at least a 90% reduction from baseline in EASI (EASI 90) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24).
- Percentage of patients with a 100% reduction from baseline in EASI (EASI 100) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24).
- Change in IGA from baseline to Day 169 (Week 24) and over time.
- Percentage of patients with a response of IGA 0 or 1 and a reduction from Baseline of ≥2 points at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12) and 141 (Week 20).
- Absolute and percentage change in SCORAD Index from baseline to Day 169 (Week 24) and over time.
- Absolute and Percentage change in affected BSA from baseline to Day 169 (Week 24) and over time.
- Absolute and Percentage change in POEM from baseline to Day 169 (Week 24) and over time.
- Absolute and Percentage change in DLQI from baseline to Day 169 (Week 24) and over time.
- Absolute and Percentage change in ADCT from baseline to Day 169 (Week 24) and over time.
- Absolute and Percentage change in HADS from baseline to Day 169 (Week 24) and over time.
- Absolute and Percentage change in weekly average of pruritus NRS from baseline to Day 169 (Week 24) and over time.

- Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ⩾3 with a baseline pruritis NRS of ⩾3 from baseline to Days 113 (Week 16) and 169 (Week 24).
- Time to loss of EASI 75 in patients randomized to withdrawal post-Week 24.
- Time to loss of IGA 0/1 in patients randomized to withdrawal post-Week 24.
- Time to loss of EASI 50 in patients randomized to withdrawal post-Week 24.

The analysis of the additional secondary endpoints analysis will be performed using the FAS set.

Analysis of other continuous secondary endpoints

For each of the other continuous secondary endpoint, the following by visit summary tables will be provided.

- Summary table at each scheduled visit up to Week 24 [redacted] Mean difference with 95% CI and p-value will be provided.
- Summary table at each scheduled visit up to Week 24 [redacted]
- Summary table at each scheduled visits from Week 24 onwards, [redacted] The change value (or percent change value) is calculated using Week 0 baseline value. Summary is presented using Week 24 re-randomization treatment arms.
- Summary table at each scheduled visits from baseline to Week 52, [redacted] The change value (or percent change value) is calculated using Week 0 baseline value. Summary is presented using Week 24 re-randomization treatment arms.
- Summary table at each scheduled visit from Week 24 onwards, [redacted] The change value (or percent change value) is calculated using Week 0 baseline value. Summary is presented using Week 24 re-randomization treatment arms.
- Summary table at each scheduled visit from baseline up to Week 52, [redacted] The change value (or percent change value) is calculated using Week 0 baseline value. Summary is presented using Week 24 re-randomization treatment arms.

[redacted]

For each of the other continuous secondary endpoint, the following line plots will be provided:

- Line plot will be provided including scheduled visits up to Week 24 using the LSMEAN estimation from the above by visit summary table.
- Line plot will be provided including scheduled visits from Week 24 up to Week 52 among patients in Part 2 using the mean change (or percent change) estimation from the above by visit summary table [redacted] The change value (or percent change value) is calculated using Week 0 baseline value. The line plot will be presented using Week 24 re-randomization treatment arms.
- Line plot will be provided including scheduled visits from baseline up to Week 52 among patients in Part 2 using the mean change (or percent change) estimation from the above by visit summary table [redacted] The change value (or percent change value) is calculated using Week 0 baseline value. The line plot will be presented using Week 24 re-randomization treatment arms .

Analysis of other categorical secondary endpoints

For each of the other categorical secondary endpoints, the following by visit summary tables will be provided.

- Summary table at each scheduled visit up to Week 24 [redacted] Proportion difference with 95% CI and p-value will be provided.
- Summary table at each scheduled visit up to Week 24 [redacted]
- Summary table at each scheduled visits from Week 24 onwards, [redacted]

[redacted] Summary is presented using Week 24 re-randomization treatment arms.

- Summary table at each scheduled visits from Week 24 onwards, [redacted] Summary is presented using Week 24 re-randomization treatment arms.
- Summary table at each scheduled visits from baseline to Week 52, [redacted]. Summary is presented using Week 24 re-randomization treatment arms.
- Summary table at each scheduled visit from Week 24 onwards, [redacted] Summary is presented using Week 24 re-randomization treatment arms.
- Summary table at each scheduled visit from baseline to Week 52, [redacted] Summary is presented using Week 24 re-randomization treatment arms.
- A summary of percentage of patients with at least a 75% reduction from baseline in EASI (EASI 75) and percentage of patients with response of IGA 0 or 1 will be presented from Week 24 to Week 52 by Part 1 rescue medications and/or prohibited medications/procedures impacting efficacy use (yes or no).

For each of the other categorical secondary endpoint, the following line plots will be provided:

- Bar plot will be provided including scheduled visits up to Week 24 [redacted]
- Bar plot will be provided including scheduled visits from Week 24 onwards, [redacted] It will be presented using Week 24 re-randomization treatment arms.
- Bar plot will be provided including scheduled visits from Week 24 onwards, [redacted] It will be presented using Week 24 re-randomization treatment arms.
- Bar plot will be provided including scheduled visits from baseline to Week 52 for patients in Part 2, [redacted]

[redacted] It will be presented using Week 24 re-randomization treatment arms

Analysis of time to event other secondary endpoints

Time to loss of EASI 75, IGA 0/1, and EASI 50 in patients who re-randomized to Part 2 will be summarized. Kaplan-Meier curves will be presented by the re-randomized treatment groups. When with reasonable number of patients entering each treatment arm during Part 2, two-sided log-rank test (based on stratification factors) and the corresponding p-value might be provided to compare the active treatment group vs corresponding withdrawal placebo arm. Off study treatment data up to Week 52 will be included in the analysis (treatment policy) for patients who discontinued study treatment before Week 52. [redacted] If applicable, the Kaplan-Meier estimates for the median time, the first and third quartiles might be presented along with approximate 95% CI's.

8.4 Exploratory Efficacy Endpoints

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The detailed information will be provided in a separate SAP document for the Biomarker Analysis.

9. Safety Analysis

Safety will be assessed through the collection and evaluation of AEs, including TEAEs and SAEs, AESIs, clinical laboratory assessments, physical examinations, vital sign measurements, and ECGs. All the analysis will be based on SAF1 & SAF2 for Part 1 and Part 2, respectively.

9.1 Adverse Events

The ICH E6(R2) Good Clinical Practice Guideline defines an AE as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Pre-treatment AE, treatment-emergent AE, post-treatment AE definition

The pre-treatment period is defined as the period up to first IMP administration.

The treatment-emergent (TE) period is defined as the period from the first IMP administration to the last IMP administration + 140 days.
The post-treatment period is defined as the period from the end of the treatment-emergent period onwards.

The AEs will be analyzed in the following 3 categories:
Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period.
TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period;
Post-treatment AEs: AEs that developed, worsened, or became serious during the post-treatment period.

Adverse events will be analyzed as following:

1. **Pre-treatment AEs summary**: include pre-treatment AEs from on or after screening date to before date of first IMP.
2. **TEAEs summary up to Week 24 (Treatment Period 1):** TEAEs during the period on or after 1st IMP and up to Week 24 visit or with a start date no more than 140 days after last administration of IMP in case of early treatment discontinuation in part 1.
3. **TEAEs summary from Week 24 onwards (Treatment Period 2):** TEAEs during the period from 1st IMP or rerandomization, that is, 1st IMP or rerandomization <= start date of AE <= Date of last IMP after re-randomization + 140 days;
4. **Overall TEAEs summary (Overall Treatment Period):** Date of First IMP <= start date of AE<= Date of last IMP + 140 days;
5. **Post-treatment AEs summary:** include post-treatment AEs that occur >=140 days after last IMP.

The incidence of any AEs, TEAEs and serious TEAEs tables will include only one occurrence of a PT per patient. If a patient reports the same PT multiple times, then that PT will only be incremented by one since patient counts will be presented. As with the PT, if a patient reports multiple AEs within the same SOC, then that SOC will only be incremented by one since patient counts will be presented. For tables showing incidence by SOC, PT and severity, SOC will be sorted Internationally Agreed Order. Within each SOC, PTs will be sorted in descending order of frequency on total of all treatment groups.

All AEs in the clinical trial database will be coded according to MedDRA, which will be used to summarise AEs by primary High Level Group Term (HLGT), High Level Term (HLT), System Organ Class (SOC) and Preferred Term (PT). All AEs, TEAEs and serious TEAEs tables will be displayed in listings.

9.1.1 Incidence of Adverse Events

An overall summary of AEs including the counts and percentages of patients will be presented by KY1005 treatment regimen and in the Placebo group for the study periods mentioned in Section 9.1:

- Any AE
- Any SAE
- At least 1 TEAE
- Any related TEAE
- Any severe TEAE
- Any Treatment Emergent SAE
- Any SAE Related to Study Treatment
- Any AE Leading to Treatment Discontinuation
- Any AE Leading to Study Discontinuation
- Any AE Leading to Death
- Any AESI

Below summary tables will be provided by KY1005 treatment regimen and the Placebo group using count and percentages of patients:

- Number (%) of Patients of Pre-treatment Adverse Events by SOC and PT
- Number (%) of Patients with TEAE by SOC and PT from Baseline (Week 0) up to Week 24
- Number (%) of Patients with TEAE by SOC and PT from Week 24 up to Week 68
- Number (%) of Patients with TEAE by SOC and PT from Baseline (Week 0) up to Week 68
- Number (%) of Patients of Post-treatment Adverse Events by SOC and PT
- Number (%) of Patients with TEAE by HLGT, HLT, SOC and PT from Baseline (Week 0) up to Week 24
- Number (%) of Patients with TEAE by HLGT, HLT, SOC and PT from Week 24 up to Week 68
- Number (%) of Patients with TEAE by HLGT, HLT, SOC and PT from Baseline (Week 0) up to Week 68
- SOC Number (%) of Patients of TEAEs by PT from Baseline (Week 0) up to Week 24
- Number (%) of Patients of TEAEs by PT from Week 24 up to Week 68
- Number (%) of Patients of TEAEs by PT with total incidence >=5% from Baseline (Week 0) up to Week 24
- Number (%) of Patients of TEAEs by PT with total incidence >=5% from Week 24 up to Week 68
- Number (%) of Patients of TEAEs by PT with total incidence >=5% from Baseline (Week 0) up to Week 68
- Number (%) of Patients of TEAEs by PT with total incidence from Baseline (Week 0) up to Week 24
- Number (%) of Patients of TEAEs by PT with total incidence from Week 24 up to Week 68

- Number (%) of Patients of TEAEs by PT with total incidence from Baseline (Week 0) up to Week 68
- Incidence Rate per Patient Year Exposed from Baseline (Week 0) up to Week 24
- Incidence Rate per Patient Year Exposed from Week 24 up to Week 68
- Incidence Rate per Patient Year Exposed from Baseline (Week 0) up to Week 68

All AEs and TEAEs will be presented in a listing.

A separate listing will be presented for Pre-treatment AEs (with details of Severity, Seriousness, first dose date, last dose date, if leading to study discontinuation, if leading to death, relative day of AE) and Post-treatment AEs(with details of Severity, Seriousness, first dose date, last dose date, if leading to study discontinuation, if leading to death, relative day of AE) .

9.1.2. Serious Adverse Events

Below summary tables will be provided by KY1005 treatment regimen and the Placebo group using count and percentages of patients for all study periods mentioned in Section 9.1:

- Number (%) of Patients with Serious TEAEs by SOC and PT from Baseline (Week 0) up to Week 24
- Number (%) of Patients with Serious TEAEs by SOC and PT from Week 24 up to Week 68
- Number (%) of Patients with Serious TEAEs by SOC and PT from Baseline (Week 0) up to Week 68

All SAEs will be presented in a listing.

A listing of SAEs for screen failures will be presented.

9.1.3 Relationship of Adverse Events to Study Drug

Below summary tables will be provided by KY1005 treatment regimen and in the Placebo group using count and percentages of patients:

- Number (%) of Patients with TEAEs by SOC, PT and Relationship from Baseline (Week 0) up to Week 24
- Number (%) of Patients with TEAEs by SOC, PT and Relationship from Week 24 up to Week 68
- Number (%) of Patients with TEAEs by SOC, PT and Relationship from Baseline (Week 0) up to Week 68

The relationships will be collected as the possibility that study drug caused the event i.e. the relationships are “Not Related”, “Related”.

9.1.4. Severity of Adverse Event

The severity of the AE will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE) as Grade 1, Grade 2, Grade 3. In the TEAE severity table, if a patient reported multiple occurrences of the same AE, only the most severe AE will be presented. AEs with missing severity will be presented on tables as “Unknown” but will be presented in the data listing with a missing severity.

Adverse events will be classified by the Investigator according to the following criteria:

- Mild (Grade 1 Common Terminology Criteria for Adverse Events [CTCAE]): Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2 CTCAE): Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe (≥ Grade 3 CTCAE): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. Life-threatening consequences; urgent intervention indicated; Death related to AE.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of severity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Below summary tables will be provided by KY1005 treatment regimen and in the Placebo group using count and percentages of patients:

- Number (%) of Patients with TEAEs by SOC, PT and Severity from Baseline (Week 0) up to Week 24
- Number (%) of Patients with TEAEs by SOC, PT and Severity from Week 24 up to Week 68
- Number (%) of Patients with TEAEs by SOC, PT and Severity from Baseline (Week 0) up to Week 68

9.1.5. Adverse Events Leading to Treatment Discontinuation and/ or Study Discontinuation

Below summary tables will be provided by KY1005 treatment regimen and in the Placebo group using count and percentages of patients:

- Number (%) of Patients with TEAEs leading to Treatment Discontinuation by SOC and PT from Baseline (Week 0) up to Week 24
- Number (%) of Patients with TEAEs leading to Treatment Discontinuation by SOC and PT from Week 24 up to Week 68
- Number (%) of Patients with TEAEs leading to Treatment Discontinuation by SOC and PT from Baseline (Week 0) to Week 68 based
- Number (%) of Patients with TEAEs leading to Study Discontinuation by SOC and PT from Baseline (Week 0) up to Week 24
- Number (%) of Patients with TEAEs leading to Study Discontinuation by SOC and PT from Week 24 up to Week 68
- Number (%) of Patients with TEAEs leading to Study Discontinuation by SOC and PT from Baseline (Week 0) to Week 68

All AEs leading to study drug discontinuation and study discontinuation will be listed by patients.

9.1.6. AE leading to Death

Below summary tables will be provided by KY1005 treatment regimen and in the Placebo group using count and percentages of patients:

- Number (%) of Patients with TEAEs leading to Death by SOC and PT from Baseline (Week 0) up to Week 24
- Number (%) of Patients with TEAEs leading to Death by SOC and PT from Week 24 up to Week 68
- Number (%) of Patients with TEAEs leading to Death by SOC and PT from Baseline (Week 0) to Week 68
- Number (%) of Patients with Post-Study Adverse Events leading to Death by SOC and PT

AEs leading to death will be listed by patients.

9.1.7. Adverse Event of Special Interest (AESI)

Below summary tables will be provided by KY1005 treatment regimen and in the Placebo group using count and percentages of patients:

- Number (%) of Patients with AESI by AESI category and PT from Baseline (Week 0) up to Week 24
- Number (%) of Patients with AESI by AESI category and PT from Week 24 up to Week 68
- Number (%) of Patients with AESI by AESI category and PT from Baseline (Week 0) up to Week 68
- Post-treatment AESI by AESI category and PT
- Number (%) of Patients with AESI by AESI category, PT and Severity from Baseline (Week 0) up to Week 24
- Number (%) of Patients with AESI by AESI category, PT and Severity from Week 24 up to Week 68
- Number (%) of Patients with AESI by AESI category, PT and Severity from Baseline (Week 0) up to Week 68

The safety follow-up period following early discontinuation will be considered for the period when the discontinuation occurred in terms of identifying AEs that started in it.

The following AEs are considered as AESIs:

- Systemic or localised allergic reactions that require immediate treatment
- Severe injection site reactions that last longer than 24 hours.
- Any severe or opportunistic viral, bacterial or fungal infection and/or any uncommon, unanticipated or persistent infection (viral, parasitic, bacterial, or fungal).
- Any malignancy.
- Increase in alanine transaminase (ALT) >3 × upper limit of normal (ULN); see the “Increase in ALT” flow chart in Section 17.12 (Appendix 12) of the protocol.

The special situations of:

- Symptomatic overdose (serious or non-serious) with IMP (overdose is defined as any administration that is twice or more than the intended dose administered in less than 3 weeks [21 days]) and symptomatic is defined as the event reported by the patient and/or the investigator.
- Pregnancy - discussed separately in Section 8.3 of the protocol.

All AESI will be presented in a listing

9.2 Clinical Laboratory Evaluations

All clinical laboratory summaries will be based on central laboratory data using the conventional units provided by the central laboratory. However, in listings results with both conventional and standard units will be provided.

Descriptive statistics for central laboratory safety parameters including absolute values and change from baseline values will be summarised with n, mean, SD, median, minimum and maximum values by treatment regime and by respective visits and timepoint if applicable.

Analysis of potentially clinically significant abnormality (PCSA) will be performed based on the PCSA criteria. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable. Analyses according to PCSA will be performed based on the worst value during the treatment emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs and ECG variables, the incidence of patients with at least one PCSA during the treatment-emergent period including unscheduled, early termination or safety follow-up visits will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria;

Changes in central laboratory data will also be summarized using shift tables from baseline to the worst toxicity grade.

Laboratory data collected at all visits including unscheduled, early termination or safety follow-up visits will be included in listings and will contribute to tables of shifts from baseline and in tables showing change from baseline grade to the worst toxicity grade. Unscheduled laboratory results will not be windowed for the purposes of assigning a nominal visit.

All vital sign, physical examination and ECG data including unscheduled, early termination or safety follow-up visits are mapped to analysis visits and are included in the summary.

9.2.1. Haematology

The following laboratory tests will be included in haematology summary tables: WBCC and differentials, RBCC, RDW, Hb, HCT, nucleated red blood cells, platelet count, MCH, MCHC, MCV and MPV. All hematology data will be presented by patient in a listing.

9.2.2. Serum Chemistry

The following laboratory tests will be included in clinical chemistry summary tables : albumin, sodium, potassium, chloride, bicarbonate, urea, creatinine, glucose, calcium, phosphate, ALT, AST, GGT, LDH, alkaline phosphatase, total protein, iron, total bilirubin and CPK. All chemistry data by patient will be presented in a listing.

9.2.3 Urinalysis

The following urinalysis laboratory tests will be included in summary tables: pH, protein, glucose, ketones and blood. All data by patient will be presented in a listing.

9.3. Vital Sign Measurements

Vital signs parameters include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (°C/F), and heart rate (beats/min). Summary tables by treatment group presenting observed values and changes from baseline at each scheduled post-baseline visit will be presented for vital signs by treatment group and overall. Change from baseline will only be calculated for patients having non-missing baseline and post-baseline measurements.

The incidence of PCSA in vital sign will be summarized using counts and percentages of patients by treatment groups and also will be summarized using shift tables from baseline to follow-up visits.

All vital sign data by patient will be presented in a listing. PCSA criteria will be flagged in the listing.

9.4. Physical Examination

A table will summarize physical examination results presenting counts and percentages by treatment group and overall. The incidence of clinically significant changes in physical examinations will be summarized using counts and percentages of patients with the body system as normal, abnormal not clinically significant or abnormal clinically significant. Physical examination results for all patients will be presented in a listing.

9.5. 12-lead ECG

12-lead ECG parameters include normal sinus rhythm, ventricular rate (beats/min), PR interval (msec), QRS duration (msec), QT interval (msec), QTcF interval (msec) and QTcB interval (msec). The QTcB and QTcF will be derived using the following formula:

Bazett Formula: $QTc = QT\ interval / \sqrt{(RR\ interval)}$

Fridericia Formula: $QTc = QT\ interval / (RR\ interval)^{1/3}$

RR interval = 60/ventricular rate

Absolute values and change from baseline to each scheduled post-baseline visit in ECG continuous variables will be summarized with n, mean, SD, standard error of the mean (SEM), median, minimum and maximum values by treatment group and overall. Change from baseline will only be calculated for patients having non-missing baseline and post-baseline measurements.

The number (n) and percentage (%) of patients with treatment-emergent PCSA will be summarized by different treatment groups using count and percentages of patients.

Changes in ECG data will also be summarized using shift tables .

Data listings by patient will be provided. PCSA criteria will be flagged in the listing.

9.6. Local Skin Reactions

Descriptive statistics (for diameter of erythema and induration will be provided overall and by treatment group. The counts and percentages of patients with pain, itchiness, and tenderness will be provided. All injection site reaction data by patient will be presented in a listing

9.7. Virology

Positive samples for HIV, HBsAg, HBcAb, [redacted] and hepatitis C at the Screening Visit will be listed by patient.

9.8. Other Analysis

The impact of the COVID-19 will be summarized by study treatment group and overall. The table will present the counts and percentages of patients for the following categories:

- Number (%) of Patients with COVID-19 up to Baseline (Week 0)
- Number (%) of Patients with COVID-19 from Baseline (Week 0) up to Week 24
- Number (%) of Patients with COVID-19 from Week 24 up to Week 68
- Number (%) of Patients with COVID-19 from Baseline (Week 0) to Week 68
- Number (%) of Patients with COVID-19 leading to study discontinuation from Baseline (Week 0) up to Week 24
- Number (%) of Patients with COVID-19 leading to study discontinuation from Week 24 up to Week 68
- Number (%) of Patients with COVID-19 leading to study discontinuation from Baseline (Week 0) to Week 68

- Number (%) of Patients with COVID-19 leading to study drug discontinuation from Baseline (Week 0) up to Week 24
- Number (%) of Patients with COVID-19 leading to study drug discontinuation from Week 24 up to Week 68
- Number (%) of Patients with COVID-19 leading to study drug discontinuation from Baseline (Week 0) to Week 68

All COVID-19 infection data by patient will be presented in a listing. A Separate listing will be prepared for listing COVID-19 infection data leading to study discontinuation, leading to study drug discontinuation.

10. Pharmacokinetics

All PK listings and individual concentration-time profiles will be presented using the SAF set. PK tables, mean figures and all statistical analyses will be presented using the PK set.

Population pharmacokinetic analysis will be to be conducted per separate analysis plan and reported separately.

10.1. Data Handling

Serum concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of concentration descriptive statistics.

10.2. Serum Concentrations

Blood samples will be collected at the following time points for PK assessment:

Predose (Day 1), Day 8, Day 15, Day 29, Day 57, Day 85, Day 113, Day 120, Day 141, Day 169, Day 176, Day 197, Day 225, Day 253, Day 281, Day 309, Day 337, and Day 365.

PK collections that have an actual sampling time that deviates from the predefined collection time window (± 3 days) or that are collected post-dose (except at Day 8, Day 15, Day 120 and D176) will be flagged in the data listings and excluded from the calculation of concentration summary statistics. In addition, when patients withdraw from the treatment earlier and still have PC collection at one or more later visits, the pre-dose PC data collected from 25 to 31 days post last dose (ie, corresponding to the time window of the next scheduled administration) are still included in the analysis.

Individual serum concentrations will be expressed in µg/mL and will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV%, median, minimum, and maximum) by treatment group and visit weeks. Serum concentration summaries will also be presented by ADA status (e.g. ADA positive, ADA negative), where data permit.

Individual serum concentrations will be plotted by actual time on linear scale. Mean serum concentrations will be plotted by treatment and visit weeks on linear scale with all dose levels overlaid on the same plots. Mean serum concentration plots will also be presented by ADA status (e.g. ADA positive, ADA negative), where data permit.

Serum concentrations will be reported to 3 significant figures in summary statistics except CV%, which will be reported to 1 decimal place.

10.3. Immunogenicity

All the analysis will be performed using Anti-drug Antibody Sets.

Patient's ADA status, response variable and kinetics of ADA responses (see definitions below) will be summarized on the ADA population.

Kinetics of ADA responses will be described for patients with treatment-induced ADA and for patients with treatment-boosted ADA, separately. Time to ADA onset and duration of ADA will be described with minimum, Q1, median, Q3 and maximum statistics.
Peak titer will be described with minimum, Q1, median, Q3 and maximum statistics for patients with treatment-induced ADA and for patients with treatment-boosted ADA, separately.

Sample status (negative, positive, inconclusive) will be described using descriptive statistics.

The impact of positive immune response on efficacy, PK and safety variables may be further explored, depending on ADA incidence.

Patient's ADA status

- Patients with **pre-existing ADA**s correspond to patients with ADAs present in samples drawn before first administration of intervention. Patients with missing ADA sample at baseline will be considered as without pre-existing ADA.
- Patients with **treatment-emergent ADA** correspond to patients with at least one treatment-induced/boosted ADA.
- Patients with **treatment-induced ADA**s correspond to patients with ADAs that developed during the treatment-emergent (TE) period and without pre-existing ADA (including patients without pre-treatment samples).
- Patients with **treatment-boosted ADA**s correspond to patients with pre-existing ADAs that are boosted during the TE period to a significant higher titer than the baseline. A 2-fold serial dilution schema is used during titration, so at least a 4-fold increase will be considered as significant.
- Patients with **unclassified ADA** correspond to patients with pre-existing ADAs that cannot be classified as treatment-boosted ADA because of missing titer(s) (ie, a positive ADA sample during the TE period in a patient with pre-existing ADA but with missing titer at this sample or at baseline).

- Patients **without treatment-emergent ADA** correspond to patients without treatment-induced/boosted ADA and without any inconclusive sample nor unclassified ADA during the TE period.
- Patients **with inconclusive ADA** are defined as patients which cannot irrefutably be classified as with or without treatment-emergent ADA.

Kinetics of ADA response

Kinetics of ADA response will be derived for patients with treatment-induced/boosted ADA considering ADA samples collected during the TE period and post-treatment period.

- Time to onset of ADA response is defined as the time period between the first IMP administration and the first treatment-induced/boosted ADA.
- Duration of ADA response is defined as the time between the first treatment-induced/ boosted ADA and the last treatment-induced/boosted ADA, irrespective of negative samples or positive samples not reaching the boosted threshold in-between. ADA duration will be summarized only for patients with persistent ADA response.
- Persistent ADA response is defined by treatment-induced/boosted ADA with a duration of ADA response of at least 16 weeks.
- Transient ADA response is defined by treatment-induced/boosted ADA with a duration of ADA response of less than 16 weeks and the last sample of the TE period is not treatment-induced/boosted.
- Indeterminate ADA response is defined by treatment-induced/boosted ADA that are neither persistent nor transient.

ADA response variable:

- ADA incidence is defined as the proportion of patients found to have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response (treatment-boosted ADAs) at any time point during the TE period.

10.4. Serum Pharmacokinetic Parameters

Not applicable.

10.5. Pharmacokinetic Statistical Analysis

Not applicable.

[redacted]

12. Interim Analysis

An interim analysis will be performed when approximately [redacted] patients in each arm complete the Week 16 assessments accounting for “no dropouts”.

The IA data cut-off date will be defined as the date when approximately [redacted] participants in each of the 5 treatment arms (500 mg loading dose + 250 mg Q4W, 250 mg Q4W, 125 mg Q4W, 62.5 mg Q4W and Placebo Q4W) have completed 16 weeks of treatment in the study.

For Interim Analysis, the interim analysis subject list will be based on the analysis population consisting of 2 sets of patients: (1) the randomized patients who complete the Week 16 visit; (2) the randomized patients who discontinue study before Week 16, but were randomized in the study early enough that the patients could have completed Week 16 visit by IA data cut-off date if not early discontinued. [redacted]

The below analysis sets will only be used for the Interim Analysis and will contain subjects from the respective analysis sets defined in Section 4.3 who are also in the interim analysis subject list:

- IA-Full Analysis Set for Part 1
- IA-Full Analysis Set for Part 2
- IA-Pharmacokinetic Set for Part 1
- IA-Pharmacokinetic Set for Part 2
- IA-Anti-drug Antibody Set for Part 1
- IA-Anti-drug Antibody Set for Part 2

The above analysis sets will be used for summaries of demographics and baseline characteristics, medical history, rescue medication and prior/concomitant medications and procedures, efficacy analyses, pharmacokinetics and immunogenicity. For the other analyses, the patients included in the analysis will correspond to the already defined analysis set, such as SAF1, SAF2, etc by the date of interim analysis data cut-off. For disposition, all patients enrolled by IA data cut-off date will be summarized.

For the interim analysis, the below parameters will be evaluated:

- Disposition of Patients
- Demographics and Baseline Characteristics
- Disease-Specific History, Medical history
- Prior & Concomitant Medications and procedures
- Rescue Medication
- Efficacy parameters, e.g. including but not limited to EASI, IGA, NRS etc
- Drug exposure
- Adverse events
- Laboratory values, ECG, Vital signs, Physical examination, Local Skin Reactions,[redacted]
- Pharmacokinetics
- Immunogenicity

[redacted]

[redacted] Statistical analysis as detailed in above sections of the SAP will be included as per requirement.

In order to maintain the further double-blinded conduct of the study, the Study Team will be kept blinded on the individual patient's treatment group assignment. There will be two separate teams at PPD for the analysis of the data. The blinded team will be performing the analyses with the dummy treatment assignment. The unblinded statistician team will be performing the analyses with the actual treatment assignment. Both the teams will be working in a separate study folder. Also, the blinded team will not have any access to the unblinded team study folders.

13. Final Analysis

The Final Analysis will be split into two phases, with an analysis performed once all subjects finish Week 52 visit i.e. Part 2 of the trial: Week 52 Analysis; and a second one once all subjects finish Week 68 i.e. Safety Follow-up period of Part 2: Week 68 analysis.

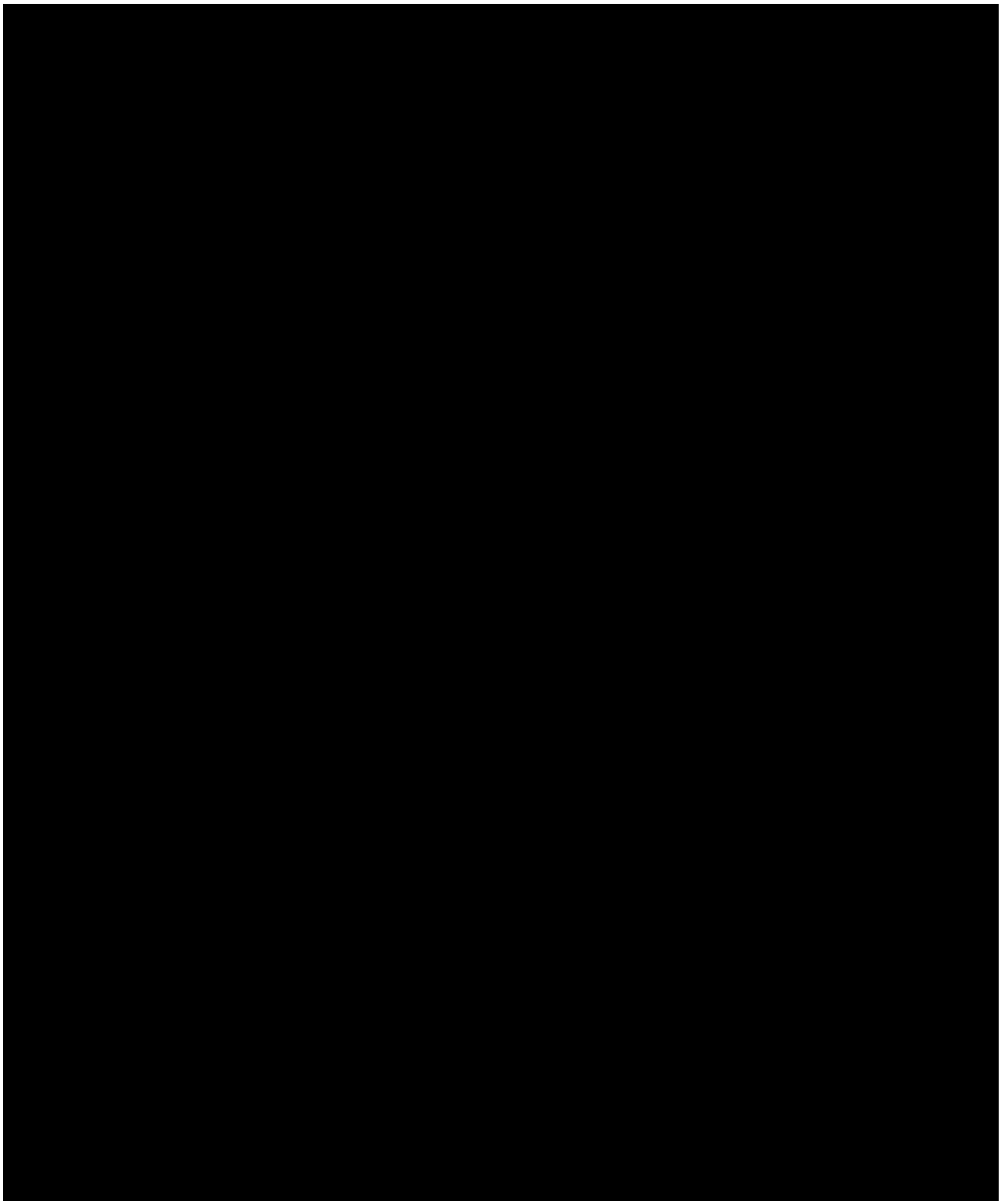
13. Changes in the Planned Analysis

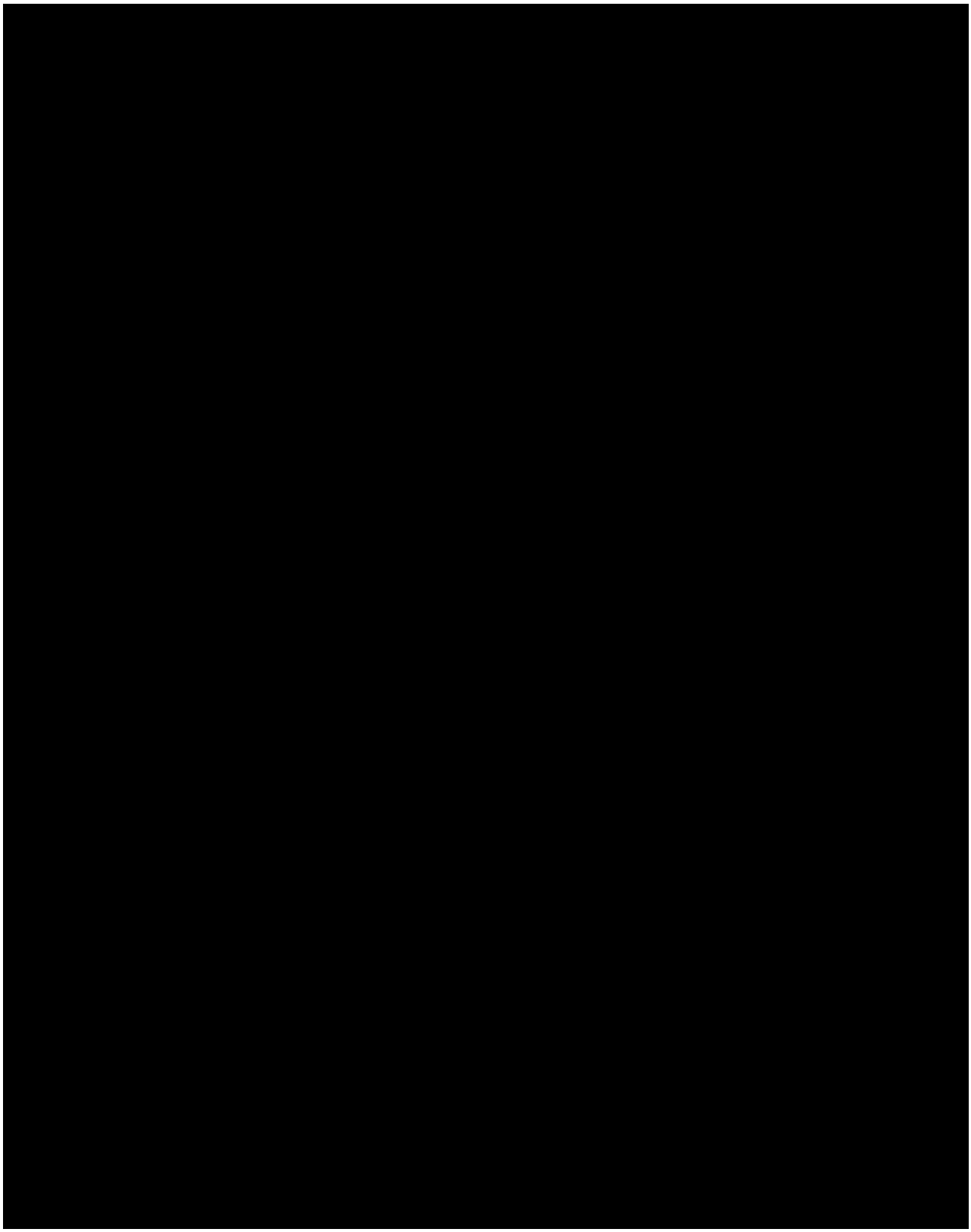
14. References

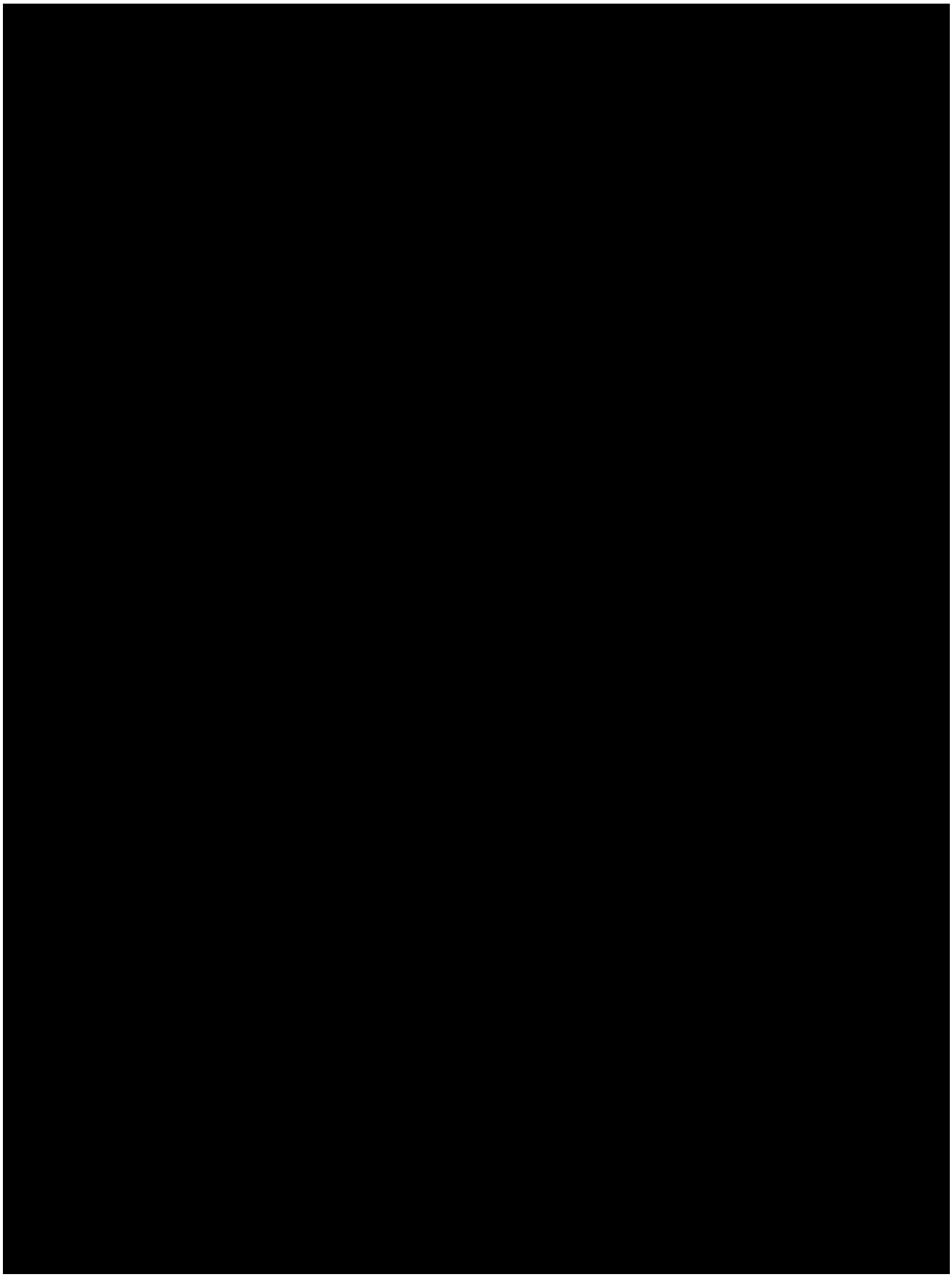
- KY1005/SAR445229-KY1005-CT05/DRI17366 Protocol Version 1.0, 01MAR2022 Amendment number: 08

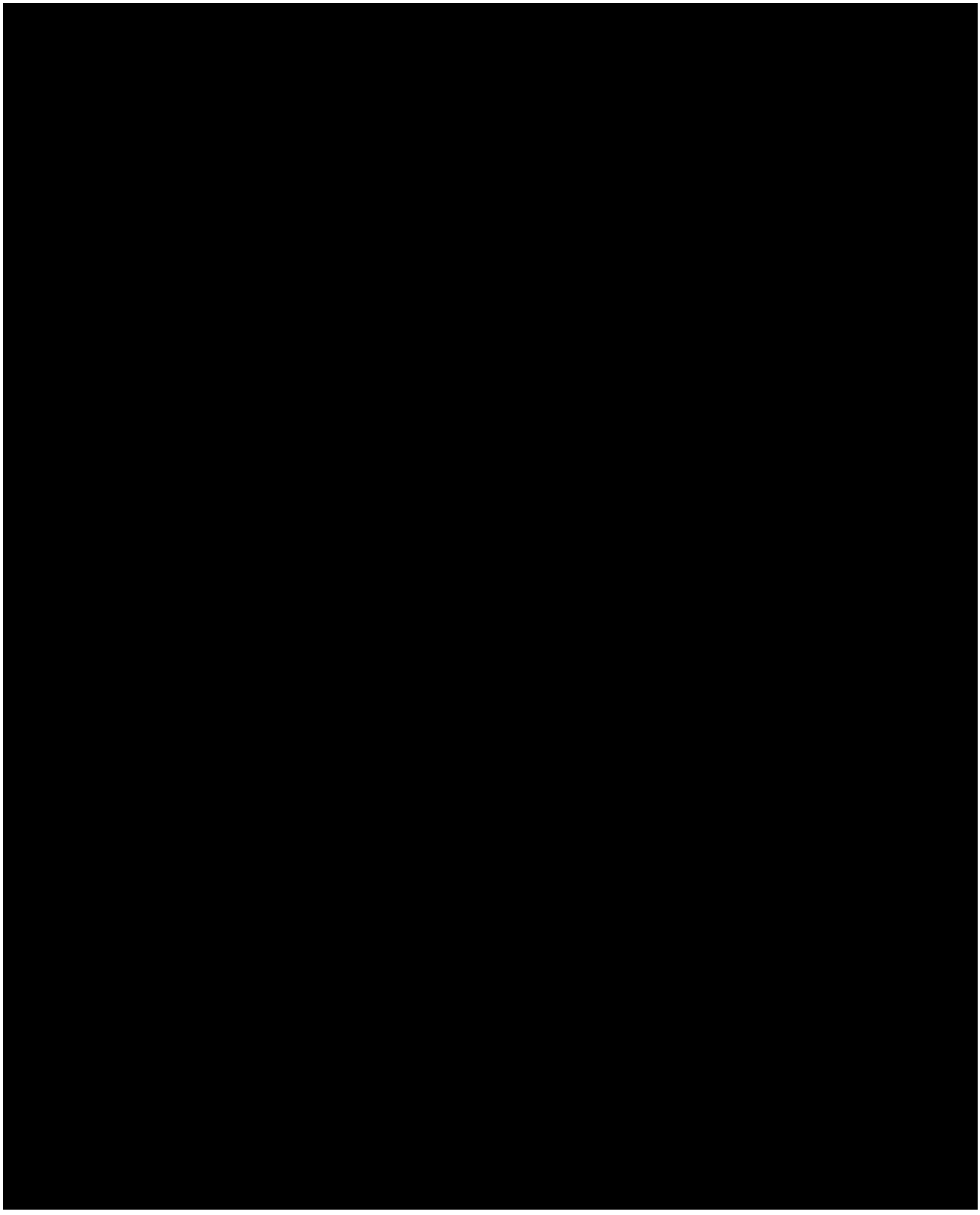
15. Appendices

15.1. Secondary Estimands and Strategies









15.2. Imputation Algorithm for Partial and Missing Dates and Time

Medications and Procedures

Impute partial/missing start date with earliest possible date, and end date with latest possible date.

If start date is completely missing in which the day, month, and year are all unknown, then the start date will not be imputed.

For the partial start date,

- If the year is present and the month and day are missing, set month and day to January 1st.
- If the year and month are present and the day is missing and year and month are equal to year and month of first dose, set day to the first dose day.
- If the year and month are present and the day is missing and year and month are not equal to year and month of first dose, set to 1st day of month.

If the end date is completely missing, in which the day, month, and year are all unknown, then the end date will not be imputed.

For the partial end date,

- If the year is present and the month and day are missing, set month and day to December 31st.
- If the year and month are present and the day is missing, set day to last day of the month.

Medications/Procedures with both missing start and end date after imputation will be considered as concomitant.

Adverse Event

If onset date is completely missing, onset date is set to date of first dose.

If year is present and month and day are missing:
If year = year of first dose, then set month and day to month and day of first dose
If year < year of first dose, then set month and day to December 31st.
If year > year of first dose, then set month and day to January 1st.

If month and year are present and day is missing:
If year = year of first dose and
If month = month of first dose then set day to day of first dose
If month < month of first dose then set day to last day of month
If month > month of first dose then set day to first day of month
If year < year of first dose then set day to last day of month
If year > year of first dose then set day to first day of month

For AEs with completely missing onset date and end date; and for AEs with completely missing onset date and the end date is on or after the first dose of study drug will considered TEAE.

15.3. Schedule of Study Procedures

Table 6 Schedule of Assessments Screening to Day 113(Week 16)

Visit	**1**		**2[b]**	**3**	**4**	**5**	**6[a]**	**7[a]**	**8[a]**	**9[a]**	**ET[#]**
Visit days	**-29 to -8**	**-7 to 1**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**-**
Visit weeks	**-4 to -1**	**- 1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**-**
Visit window (days)	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**
	Screening		**Baseline**	**Treatment**							
Description	**Clinic**		**Clinic**	**Clinic**	**Clinic**	**Telephone[m]** Error! Reference source not found.	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Informed consent	X										
Demographics	X										
Medical history	X										
Concomitant medications - including emollients	X		X[a]	X	X	X	X	X	X	X	X
AEs (including SAEs)	<==========									==========>	X
Inclusion/exclusion criteria	X		X								
Physical examination	X		X		X		X	X	X	X	X
Body weight and height (height at Screening only)	X		X							X	X
Vital signs[c]	X		X				X	X	X	X	X
12-lead ECG	X		X					X		X	X
EASI	X		X		X		X	X	X	X	X
BSA	X		X		X		X	X	X	X	X
IGA	X		X		X		X	X	X	X	X

Visit	**1**		**2[b]**	**3**	**4**	**5**	**6[a]**	**7[a]**	**8[a]**	**9[a]**	**ET[#]**
Visit days	**-29 to -8**	**-7 to 1**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	-
Visit weeks	**-4 to -1**	**- 1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	-
Visit window (days)	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	-
	Screening		**Baseline**	**Treatment**							
Description	**Clinic**		**Clinic**	**Clinic**	**Clinic**	**Telephone[m]** Error! Reference source not found.	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
SCORAD Index[i]	X		X				X	X	X	X	X
DLQI[i]			X		X			X		X	X
ADCT[i]			X							X	X
HADS[i]			X					X		X	X
Blood samples for virology (HIV, Hepatitis B and C) and TB (QuantiFERON®-TB Gold blood test)[Error! Reference source not found.]	X										
Safety tests (FBC, non-fasting biochemistry, electrolytes, urinalysis), FSH for post-menopausal women at Screening	X[k]		X				X	X	X	X	X
Pregnancy test – females only (serum at Screening, urine thereafter)[e]	X		X				X	X	X	X	X
Blood samples for serum concentrations of KY1005 (PK)[a]			X[a]	X	X		X	X	X	X	X
Blood samples for serum concentrations of ADAs[d]	[redacted]										

Visit	**1**		**2[b]**	**3**	**4**	**5**	**6[a]**	**7[a]**	**8[a]**	**9[a]**	**ET[#]**
Visit days	**-29 to -8**	**-7 to 1**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	-
Visit weeks	**-4 to -1**	**- 1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	-
Visit window (days)	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	-
	Screening		**Baseline**	**Treatment**							
Description	**Clinic**		**Clinic**	**Clinic**	**Clinic**	**Telephone[m]Error! Reference source not found.**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
POEM[i]			X				X	X	X	X	X
NRS (pruritus) – internet-enabled device[g]		X[h]Error! Reference source not found.	X	→	→	→	→	→	→	→	→
Contact IRT	X		X	X	X	X	X	X	X	X	X
Randomisation[i]Error! Reference source not found.			X								
IMP administration and check of local skin reaction[j,o]			**X**				X	X	X	X	

[redacted]

[redacted]

Index; ECG=electrocardiogram; FBC=full blood count; FSH=follicle-stimulating hormone; HADS= Hospital Anxiety and Depression Scale; HIV=human immunodeficiency virus; IgE=immunoglobulin E; IMP=Investigational Medicinal Product; NRS=Numerical Rating Scale; POEM=Patient Oriented Eczema Measure; PK=pharmacokinetics; PRO=patient reported outcome; SAE=serious adverse event; SCORAD=SCORing of Atopic Dermatitis; TB=tuberculosis; IGA= Investigator Global Assessment.

Early Termination could be done by the Investigator (see Section 3.4, Section 3.5 and Section 9 of protocol).

a On IMP administration days, all assessments, including taking blood samples, will be performed pre-injection unless stated otherwise.

b Baseline assessments may be performed up to 24 hours prior to the first IMP injection (Day 1).

c On IMP administration days up to and including Day 113 (Week 16) vital signs will be measured pre-injection and at 15-, 30- and 60-minutes post-injection. The tolerance on vital signs measurements after dosing is ±5 minutes.

d [redacted]

e If urine pregnancy test is positive, a serum control must be done before IMP administration

f [redacted]

g NRS (pruritus) will be recorded daily, ideally in the morning, based on the previous 24 hours, with worst (maximum) itch intensity recorded.

h Patients will be asked to assess their worst itching due to atopic dermatitis over the last 7 days prior to Baseline on an NRS anchored by the terms “no itch” (0) and “worst itch imaginable” (10).

i May be performed up to 24 hours prior to first injection as long as all inclusion/exclusion criteria are satisfied.

j [redacted]

k Screening laboratory assessments may be repeated a maximum of once where initial results are in the Investigator's opinion, clinically significant

l Where possible, the PRO assessments completed at the study site are to be completed by patients prior to the completion of other study assessments and the administration of IMP.

m A telephone visit is defined as a videoconference, video call or telephone call.

n [redacted]

o [redacted]

Table 7 Schedule of Assessments - Day 120 (Week 17) to Day 169(Week 24)

Visit	**10**	**11[a]**	**12**	**13**	**14**	**15[a]**	**ET[#]**
Visit days	**120**	**141**	**148**	**155**	**162**	**169**	-
Visit weeks	**17**	**20**	**21**	**22**	**23**	**24[k]**	-
Visit window (days)	**±1**	**±3**	**±1**	**±1**	**±1**	**±3**	-
	Treatment						-
Description	**Clinic**	**Clinic**	**Telephone[h]**	**Telephone[h]**	**Telephone[h]**	**Clinic**	**Clinic**
Concomitant medications – including emollients	X	X	X	X	X	X	X
AEs (including SAEs)	<==========					==========>	X
Physical examination							X
Vital signs[b]		X				X	X
12-lead ECG						X	X
EASI		X				X	X
BSA		X				X	X
IGA		X				X	X
SCORAD Index[g]		X				X	X
DLQI[g]		X				X	X
ADCT[g]						X	X
HADS[g]		X				X	X
Safety tests (FBC, non-fasting biochemistry, electrolytes, urinalysis)		X				X	X
Pregnancy test - females only (urine)[i]		X				X	X
Blood samples for serum concentrations of KY1005 (PK)[a]	X	X				X	X

Visit	**10**	**11**[a]	**12**	**13**	**14**	**15**[a]	**ET**[#]
Visit days	**120**	**141**	**148**	**155**	**162**	**169**	-
Visit weeks	**17**	**20**	**21**	**22**	**23**	**24**[k]	-
Visit window (days)	**±1**	**±3**	**±1**	**±1**	**±1**	**±3**	-
	Treatment						-
Description	**Clinic**	**Clinic**	**Telephone**[h]	**Telephone**[h]	**Telephone**[h]	**Clinic**	**Clinic**
Blood samples for serum concentrations of ADAs[c]	[redacted]						
POEM[g]		X				X	X
NRS (pruritus) – internet-enabled device[d]	→	→	→	→	→	→	→
Contact IRT	X	X	X	X	X	X	X
Re-randomisation						X[e]	
IMP administration and check of local skin reaction[f, g, j]		**X**				X	

ADA=anti-drug antibody; ADCT=atopic dermatitis control tool; AEs=adverse events; BSA=body surface area; DLQI=Dermatology Quality of Life Index; EASI=Eczema Area and Severity Index; ECG=electrocardiogram; FBC=full blood count; IgE=immunoglobulin E; IMP=Investigational Medicinal Product; NRS=Numerical Rating Scale; POEM=Patient Oriented Eczema Measure; PK=pharmacokinetics; PRO=patient reported outcome; SAE=serious adverse event; SCORAD=SCORing of Atopic Dermatitis; IGA= Investigator Global Assessment; HADS= Hospital Anxiety and Depression Scale.

\# Early Termination Visit could be done by the Investigator (see Section 3.4, Section 3.5 and Section 9 of protocol).

a On IMP administration days, all assessments, including taking blood samples, will be performed pre-injection unless stated otherwise.

b On IMP administration days vital signs will be measured pre-injection and 30 minutes post injection. The tolerance on vital signs after dosing is ±5 minutes.

c [redacted]

d NRS (pruritus) will be recorded daily, ideally in the morning, based on the previous 24 hours with worst (maximum) itch intensity recorded.

e Where IMP administration occurs on a re-randomisation day the IMP injection is to be administered after re-randomisation (with the new regimen where applicable).

f [redacted]

g Where possible, the PRO assessments completed at the study site are to be completed by patients prior to the completion of other study assessments and the administration of IMP.

h A telephone visit is defined as a videoconference, video call or telephone call.

i If urine pregnancy test is positive, a serum control must be done before IMP administration

j [redacted]

k The ICF from the DRI/Phase2b/parent study will not be valid as LTE informed consent. In order for patients to roll over to the LTE study, a specific LTE ICF will need to be applied, agreed upon and signed at the LTE study, as the LTE is a separated protocol.

Table 8 Schedule of Assessments - Day 176 (Week 25) to Day 365(Week 52)

Visit	**16**	**17[a]**	**18**	**19[a]**	**20**	**21[a]**	**22[a]**	**23**	**24[a]**	**25**	**26[a]**	**27**	**28[a]**	
Visit days	**176**	**197**	**204**	**225**	**232**	**253**	**281**	**288**	**309**	**316**	**337**	**344**	**365**	
Visit weeks	**25[i]**	**28[i]**	**29[i]**	**32[i]**	**33[i]**	**36[i]**	**40[i]**	**41[i]**	**44[i]**	**45[i]**	**48[i]**	**49[i]**	**52[i]**	**ET[#]**
Visit window (days)	**±1**	**±3**	**±1**	**±3**	**±1**	**±3**	**±3**	**±1**	**±3**	**±3**	**±3**	**±1**	**±3**	
	Treatment													**-**
Description	**Clinic**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Clinic**
Concomitant medications - including emollients	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs (including SAEs)	<========== ========>													X
Physical examination		X					X						X	X
Vital signs[b]		X		X		X	X		X		X		X	X
12-lead ECG				X			X				X		X	X
EASI		X		X		X	X		X		X		X	X
BSA		X		X		X	X		X		X		X	X
IGA		X		X		X	X		X		X		X	X
SCORAD Index[g]		X		X		X	X		X		X		X	X
DLQI[g]		X		X		X	X		X		X		X	X
ADCT[g]						X							X	X

Visit	**16**	**17[a]**	**18**	**19[a]**	**20**	**21[a]**	**22[a]**	**23**	**24[a]**	**25**	**26[a]**	**27**	**28[a]**	**ET[#]**
Visit days	**176**	**197**	**204**	**225**	**232**	**253**	**281**	**288**	**309**	**316**	**337**	**344**	**365**	
Visit weeks	**25[i]**	**28[i]**	**29[i]**	**32[i]**	**33[i]**	**36[i]**	**40[i]**	**41[i]**	**44[i]**	**45[i]**	**48[i]**	**49[i]**	**52[i]**	
Visit window (days)	**±1**	**±3**	**±1**	**±3**	**±1**	**±3**	**±3**	**±1**	**±3**	**±3**	**±3**	**±1**	**±3**	
	Treatment													**-**
Description	**Clinic**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Clinic**
HADS[g]		X		X		X	X		X		X		X	X
Safety tests (FBC, non-fasting biochemistry, electrolytes, urinalysis)		X		X		X	X		X		X		X	X
Pregnancy test - females only (urine)[i]		X		X		X	X		X		X		X	X
Blood samples for serum concentrations of KY1005 (PK)[a]	X	X		X		X	X		X		X		X	X
Blood samples for serum concentrations of ADAs[c]	[redacted]													

Visit	**16**	**17[a]**	**18**	**19[a]**	**20**	**21[a]**	**22[a]**	**23**	**24[a]**	**25**	**26[a]**	**27**	**28[a]**	**ET[#]**
Visit days	**176**	**197**	**204**	**225**	**232**	**253**	**281**	**288**	**309**	**316**	**337**	**344**	**365**	
Visit weeks	**25[i]**	**28[i]**	**29[i]**	**32[i]**	**33[i]**	**36[i]**	**40[i]**	**41[i]**	**44[i]**	**45[i]**	**48[i]**	**49[i]**	**52[i]**	
Visit window (days)	**±1**	**±3**	**±1**	**±3**	**±1**	**±3**	**±3**	**±1**	**±3**	**±3**	**±3**	**±1**	**±3**	
	Treatment													**-**
Description	**Clinic**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Clinic**
[redacted]														
POEM[g]				X		X	X		X		X		X	X
NRS (pruritus) - internet-enabled device[d]	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP administration and check of local skin reaction[e]		**X**		**X**		**X**	**X**		**X**		**X**			

ADAs=anti-drug antibodies; ADCT=atopic dermatitis control tool; AEs=adverse events; BSA=body surface area; DLQI=Dermatology Quality of Life Index; EASI=Eczema Area and Severity Index; ECG=electrocardiogram; FBC=full blood count; IgE=immunoglobulin E; IMP=Investigational Medicinal Product; NRS=Numerical Rating Scale; POEM=Patient Oriented Eczema Measure; PK=pharmacokinetics; PRO=patient reported outcome; SAE=serious adverse event; SCORAD=SCORing of Atopic Dermatitis; IGA= Investigator Global Assessment; HADS= Hospital Anxiety and Depression Scale.

\# Early Termination could be done by the Sponsor or the Investigator (see Section 3.4, Section 3.5 and Section 9 of protocol).

a On IMP administration days in this time period, all assessments, including taking blood samples, will be performed pre-injection unless stated otherwise.

b On IMP administration days in this time period, vital signs will be measured pre-injection and 30 minutes post- injection. The tolerance on vital signs after dosing is ±5minutes.

c [redacted]

d NRS (pruritus) will be recorded daily, ideally in the morning, based on the previous 24 hours with worst (maximum) itch intensity recorded.

e [redacted]

f A telephone visit is defined as a videoconference, video call or telephone call.

g Where possible, the PRO assessments completed at the study site are to be completed by patients prior to the completion of other study assessments and the administration of IMP.

i If urine pregnancy test is positive, a serum control must be done before IMP administration.

j The ICF from the DRI/Phase2b/parent study will not be valid as LTE informed consent. In order for patients to roll over to the LTE a specific LTE ICF will need to be applied, agreed upon and signed at the LTE study, as the LTE is a separated protocol.

Table 9 Schedule of Assessments – Safety Follow-up

Visit	**29[a]**	**30[a]**	**31[a]**	**32[a]**	**ET[#]**
Visit days	**393**	**421**	**449**	**477**	
Visit weeks	**56[d]**	**60[d]**	**64[d]**	**68[d]**	
Visit window (days)	±7	±7	±7	±7	
Description	**Clinic**	**Telephone[b]**	**Clinic**	**Clinic**	**Clinic**
Concomitant medications - including emollients	X	X	X	X	X
AEs (including SAEs)	----------				X
Physical examination			X	X	X
Vital signs	X		X	X	X
12-lead ECG	X		X	X	X
Safety tests (FBC, non-fasting biochemistry, electrolytes, urinalysis)	X		X	X	X
Pregnancy test – females only (urine)[c]	X		X	X	X
Blood samples for serum concentrations of ADAs	[redacted]				

[redacted]; AEs=adverse events; ECG=electrocardiogram; FBC=full blood count; SAE=serious adverse event.

\# Early Termination could be done by the Sponsor or the Investigator (see Section 3.4, Section 3.5 and Section 9).

a For patients who are not enrolled into the LTE (LTS17367) and require additional safety follow-up.

b A telephone visit is defined as a videoconference, video call or telephone call.

c If urine pregnancy test is positive, a serum control must be done before IMP administration.

d The ICF from the DRI/Phase2b/parent study will not be valid as LTE informed consent. In order for patients to roll over to the LTE a specific LTE ICF will need to be applied, agreed upon and signed at the LTE study, as the LTE is a separated protocol.

15.4. PCSA Criteria

Table 10 Vital Signs

Vital Signs	PCSA Criteria
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg
Weight	≥5% increase from baseline ≥5% decrease from baseline

Table 11 12-Lead ECG

ECG test	PCSA Criteria
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm >90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm

PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%
QTCB, QTCF	Absolute values >450 ms >480 ms >500 ms Increase from baseline Increase from baseline]30-60] ms Increase from baseline >60 ms
QT	> 500 ms

Table 12 Clinical Laboratory Parameters

Laboratory Test	PCSA Criteria
ALT	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN
AST	By distribution analysis: >3 ULN >5 ULN

	>10 ULN >20 ULN
Alkaline Phosphatase	> 1.5 ULN
Total Bilirubin	>1.5 ULN >2 ULN
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN
CPK	>3 ULN >10 ULN
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)
Uric Acid	Hyperuricemia >408 µmol/L Hypouricemia <120 µmol/L
Blood Urea Nitrogen (BUN)	≥17 mmol/L
Chloride	<80 mmol/L >115 mmol/L
Sodium	≤129 mmol/L ≥160 mmol/L
Potassium	<3 mmol/L ≥5.5 mmol/L

Total cholesterol	≥7.74 mmol/L
Triglycerides	≥4.6 mmol/L
Lipasemia	>= 3 ULN
Amylasemia	>= 3 ULN
Glucose	Hypoglycaemia ≤3.9 mmol/L and <LLN Hyperglycaemia ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)
HbA1c	> 8%
Albumin	<= 25 g/L
CRP	>2 ULN or >10 mg/L (if ULN not provided)
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L
Lymphocytes	>4.0 Giga/L
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)
Monocytes	>0.7 Giga/L
Basophils	>0.1 Giga/L
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)
RBC	≥6 Tera/L
Platelets	<100 Giga/L ≥700 Giga/L
pH	≤4.6 ≥8

15.5 Analysis window Details

Table 13 Analyses window definition for Efficacy Parameters

Scheduled visit baseline /post baseline	Targeted study day	Analysis window in study days	Efficacy Parameters
Visit 1	0	<1	EASI, BSA, IGA, SCORAD Index, DLQI, ADCT, HADS
Baseline Week 0 (Visit 2)	1	1	EASI, BSA, IGA, SCORAD Index, DLQI, ADCT, HADS, POEM
Week 2 (Visit 4)	15	2 to 22	EASI, BSA, IGA, DLQI
Week 4 (Visit 6)	29	23 to 43	EASI, BSA, IGA, SCORAD Index, POEM
Week 8 (Visit 7)	57	44 to 71	EASI, BSA, IGA, SCORAD Index, DLQI, HADS, POEM
Week 12 (Visit 8)	85	72 to 99	EASI, BSA, IGA, SCORAD Index, POEM
Week 16 (Visit 9)	113	100 to 127	EASI, BSA, IGA, SCORAD Index, DLQI, ADCT, HADS, POEM
Week 20 (Visit 11)	141	128 to 155	EASI, BSA, IGA, SCORAD Index, DLQI, HADS, POEM
Week 24 (Visit 15)	169	156 to 183	EASI, BSA, IGA, SCORAD Index, DLQI, ADCT, HADS, POEM
Week 28 (Visit 17)	197	184 to 211	EASI, BSA, IGA, SCORAD Index, DLQI, HADS
Week 32 (Visit 19)	225	212 to 239	EASI, BSA, IGA, SCORAD Index, DLQI, HADS, POEM
Week 36 (Visit 21)	253	240 to 267	EASI, BSA, IGA, SCORAD Index, DLQI, ADCT, HADS, POEM

Week 40 (Visit 22)	281	268 to 295	EASI, BSA, IGA, SCORAD Index, DLQI, HADS, POEM
Week 44 (Visit 24)	309	296 to 323	EASI, BSA, IGA, SCORAD Index, DLQI, HADS, POEM
Week 48 (Visit 26)	337	324 to 351	EASI, BSA, IGA, SCORAD Index, DLQI, HADS, POEM
Week 52 (Visit 28)	365	> 351	EASI, BSA, IGA, SCORAD Index, DLQI, ADCT, HADS, POEM
• Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for patient not exposed). • Any visit outside the analysis window will be considered as the Unscheduled visit.			

Table 12.1 – Time window for Pruritus NRS

Analysis Visit	Day Range for Calculating Weekly Score	Target Day
Baseline (Week 0)	-6-1	1
Week 1	2-8	8
Week 2	9-15	15
Week 3	16-22	22
Week 4	23-29	29
Week 5	30-36	36
Week 6	37-43	43
Week 7	44-50	50
Week 8	51-57	57
Week 9	58-64	64
Week 10	65-71	71
Week 11	72-78	78
Week 12	79-85	85
Week 13	86-92	92
Week 14	93-99	99

Analysis Visit	Day Range for Calculating Weekly Score	Target Day
Week 15	100-106	106
Week 16	107-113	113
Week 17	114-120	120
Week 18	121-127	127
Week 19	128-134	134
Week 20	135-141	141
Week 21	142-148	148
Week 22	149-155	155
Week 23	156-162	162
Week 24	163-169	169
Week 25	170-176	176
Week 26	177-183	183
Week 27	184-190	190
Week 28	191-197	197
Week 29	198-204	204
Week 30	205-211	211
Week 31	212-218	218
Week 32	219-225	225
Week 33	226-232	232
Week 34	233-239	239
Week 35	240-246	246
Week 36	247-253	253
Week 37	254-260	260
Week 38	261-267	267
Week 39	268-274	274
Week 40	275-281	281
Week 41	282-288	288
Week 42	289-295	295

Analysis Visit	Day Range for Calculating Weekly Score	Target Day
Week 43	296-302	302
Week 44	303-309	309
Week 45	310-316	316
Week 46	317-323	323
Week 47	324-330	330
Week 48	331-337	337
Week 49	338-344	344
Week 50	345-351	351
Week 51	352-358	358
Week 52	359-365	365

Table 14 Analyses window definition for Safety Parameters

Scheduled visit baseline /post baseline	Targeted study day	Analysis window in study days	Safety Parameters
Visit 1	0	< 1	PE, VS, LAB, ECG,
Week 0 (Visit 2)	1	1	PE, VS, LAB, ECG,
Week 2 (Visit 4)	15	2 to 22	PE
Week 4 (Visit 6)	29	23 to 43	PE, VS, LAB, ECG,
Week 8 (Visit 7)	57	44 to 71	PE, VS, LAB, ECG,
Week 12 (Visit 8)	85	72 to 99	PE, VS, LAB, ECG,
Week 16 (Visit 9)	113	100 to 127	PE, VS, LAB, ECG,
Week 20 (Visit 11)	141	128 to 155	PE, VS, LAB,
Week 24 (Visit 15)	169	156 to 183	PE, VS, LAB, ECG,
Week 28 (Visit 17)	197	184 to 211	PE, VS, LAB,
Week 32 (Visit 19)	225	212 to 239	PE, VS, LAB, ECG,
Week 36 (Visit 21)	253	240 to 267	PE, VS, LAB,
Week 40 (Visit 22)	281	268 to 295	PE, VS, LAB, ECG,

Week 44 (Visit 24)	309	296 to 323	PE, VS, LAB,
Week 48 (Visit 26)	337	324 to 351	PE, VS, LAB, ECG,
Week 52 (Visit 28)	365	352 to 379	PE, VS, LAB, ECG,
Week 56 (Visit 29)	393	380 to 407	VS, LAB, ECG
Week 60 (Visit 30)	421	408 to 435	PE, VS, LAB, ECG
Week 64 (Visit 31)	449	436 to 463	PE, VS, LAB, ECG
Week 68 (Visit 32)	477	> 463	PE, VS, LAB, ECG

- Adverse events, Concomitant medications are collected from screening and throughout the study.
- Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for patient not exposed).

updated

Table 15 Analyses window definition for PK Parameters

Scheduled visit baseline /post baseline	Targeted study day	Analysis window in study days	PK Parameters
Week 0 (Visit 2)	1	1	PK, ADAs, total IgE/soluble protein
Week 1 (Visit 3)	8	5 to 11	PK
Week 2 (Visit 4)	15	12 to 22	PK, ADAs
Week 4 (Visit 6)	29	23 to 43	PK, ADAs, total IgE/soluble protein
Week 8 (Visit 7)	57	44 to 71	PK
Week 12 (Visit 8)	85	72 to 99	PK
Week 16 (Visit 9)	113	100 to 117	PK, ADAs, total IgE/soluble protein
Week 17 (Visit 10)	120	118 to 131	PK
Week 20 (Visit 11)	141	132 to 155	PK
Week 24 (Visit 15)	169	156 to 173	PK, ADAs, total IgE/soluble protein
Week 25 (Visit 16)	176	174 to 187	PK
Week 28 (Visit 17)	197	188 to 211	PK
Week 32 (Visit 19)	225	212 to 239	PK

Week 36 (Visit 21)	253	240 to 267	PK, ADAs, total IgE/soluble protein
Week 40 (Visit 22)	281	268 to 295	PK
Week 44 (Visit 24)	309	296 to 323	PK
Week 48 (Visit 26)	337	324 to 351	PK, ADAs
Week 52 (Visit 28)	365	352 to 421	PK, ADAs, total IgE/soluble protein
Week 68 (Visit 32)	477	> 421	ADAs
Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for patient not exposed). Any visit outside the analysis window will be considered as the Unscheduled visit.			

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**Kymab Ltd, a Sanofi Company**
Protocol Number:	**KY1005-CT05**

Document Description:	Final Statistical Analysis Plan
SAP Title:	A Phase IIb, Randomised, Double-blind, Placebo-controlled, Parallel Group, Multicentre Dose Ranging Study of a Subcutaneous Anti-OX40L Monoclonal Antibody (KY1005) in Moderate-to-Severe Atopic Dermatitis
SAP Version Number:	3.0
Effective Date:	21 Nov 2023

Author(s):

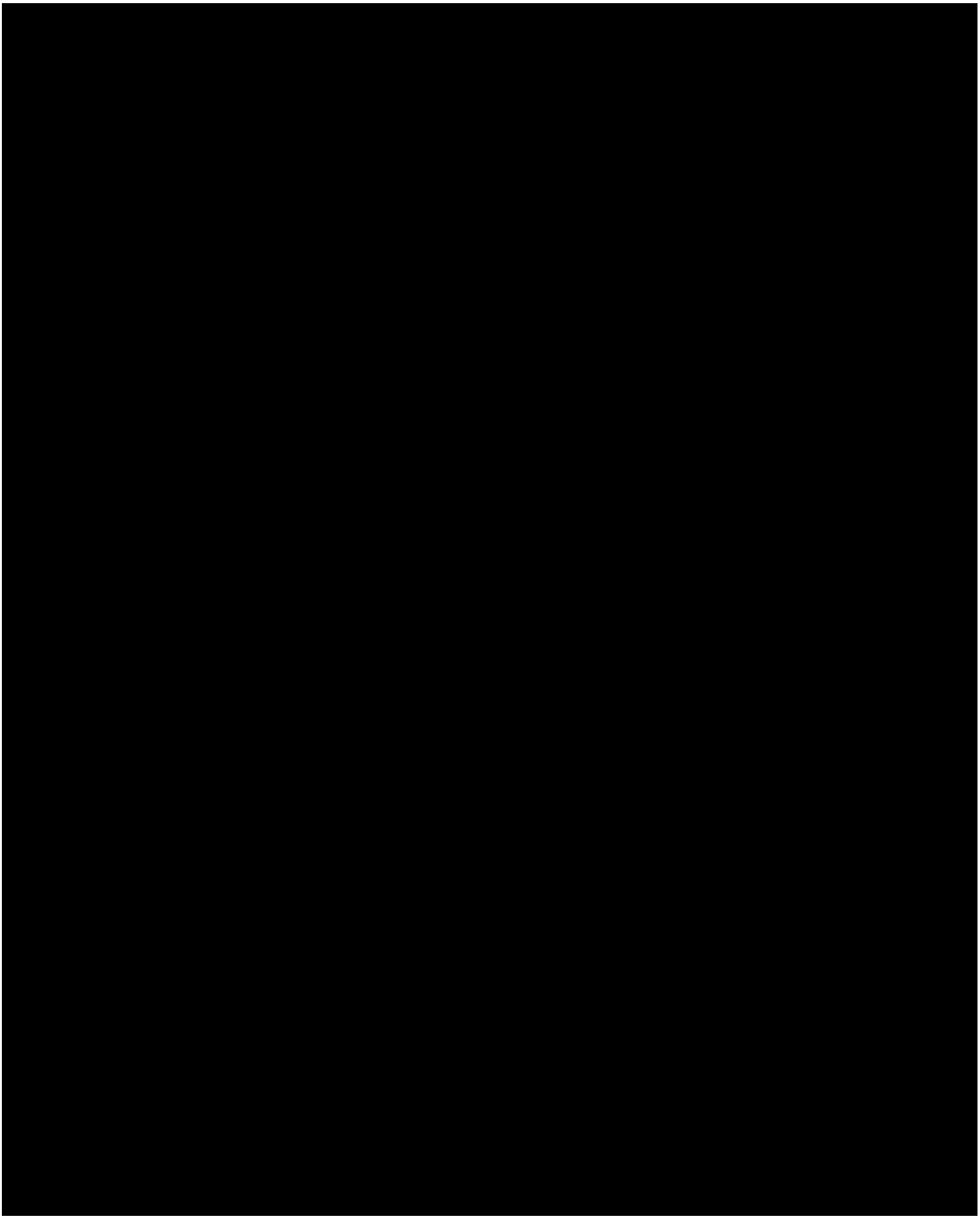
For PPD:

[redacted]

Approved by:

[redacted]

Date *(DD-MMM-YYYY)*



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